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(54) **Céphalosporines comportant en position 3 un radical propényle substitué par un ammonium quaternaire, leur procédé de préparation, leur application comme médicaments, les compositions les renfermant et les intermédiaires obtenus**

Cephalosporine mit in der Lage 3 ein Propenylradikal, substituiert durch eine quaternäre Ammoniumgruppe, ihr Verfahren zur Herstellung, ihre Anwendung als Medikamente, ihre sie enthaltende Präparate und ihre Zwischenprodukte

Cephalosporins having in position 3 a propenyl radical substituted by a quaternary ammonium, their process for preparation, their use as medicaments, compositions containing them and intermediates

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(73) Titulaire: **HOECHST MARION ROUSSEL**  
**92800 Puteaux (FR)**

(72) Inventeurs:

- **Aszodi, Jozsef**  
**F-94600 Choisy le Roi (FR)**
- **Chantot, Jean-François**  
**F-77410 Gressy en France (FR)**
- **Gouin d'Ambrieres, Solange**  
**F-75020 Paris (FR)**

(74) Mandataire: **Vieillefosse, Jean-Claude et al**  
**Hoechst Marion Roussel**  
**Département des Brevets**  
**102, Route de Noisy**  
**93235 Romainville Cédex (FR)**

(56) Documents cités:

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<b>EP-A- 0 315 518</b>	<b>EP-A- 0 333 154</b>
<b>WO-A-87/03875</b>	<b>GB-A- 2 134 522</b>
<b>GB-A- 2 157 293</b>	

Remarques:

Le dossier contient des informations techniques présentées postérieurement au dépôt de la demande et ne figurant pas dans le présent fascicule.

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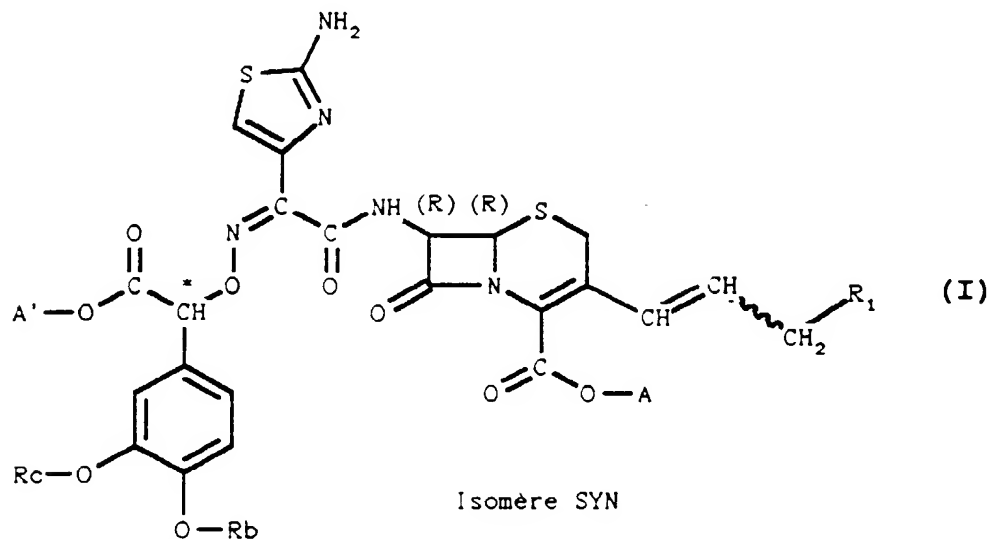
**EP 0 462 009 B1**

## Description

La présente invention concerne de nouvelles céphalosporines comportant en position 3 un radical propényle substitué par un ammonium quaternaire, leur procédé de préparation, leur application comme médicaments, les compositions les renfermant et les nouveaux intermédiaires obtenus.

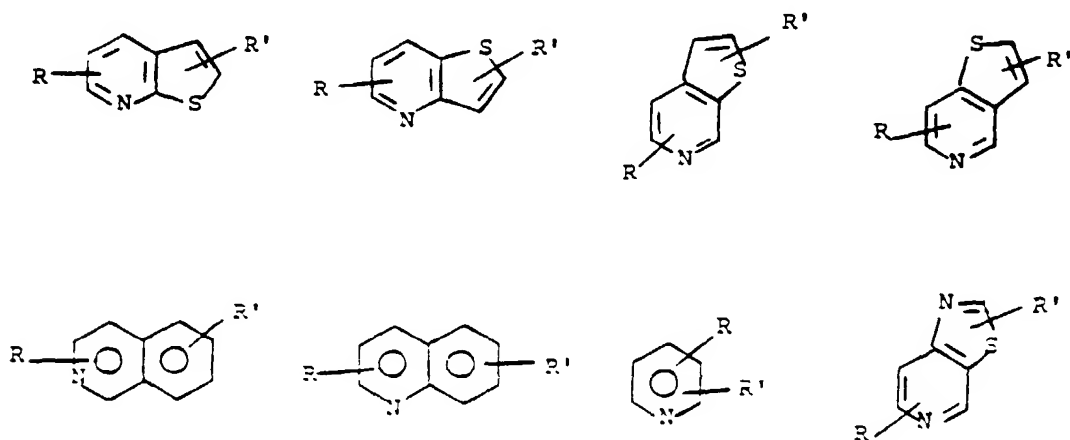
On connaît par les documents cités ci-après, à savoir GB-A-2 157293, GB-A-2 134522, EP-A-0 266060, EP-A-0 315518, EP-A-0 333154, EP-A-0 264091 et WO-A-87/03875, des composés de type céphalosporines comportant en 7 une chaîne latérale amino thiazolyl acétamido substituée par une fonction alkyle oxime elle-même éventuellement substituée, et en 3, notamment un radical propényle substitué par un ammonium quaternaire, composés possédant des propriétés antibactériennes.

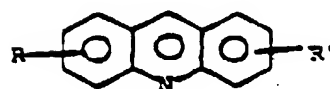
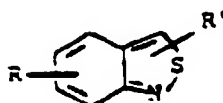
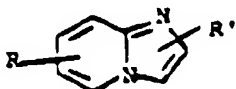
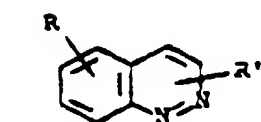
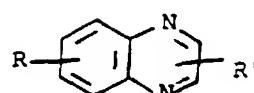
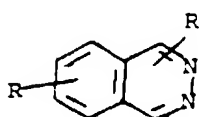
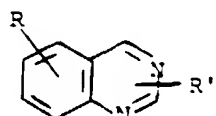
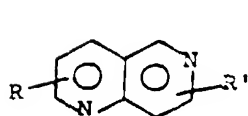
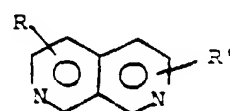
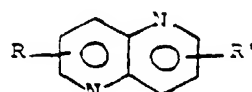
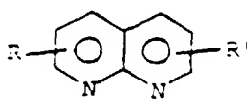
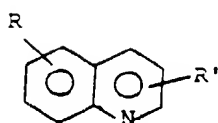
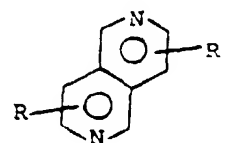
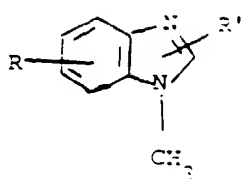
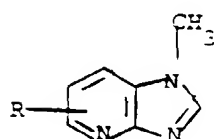
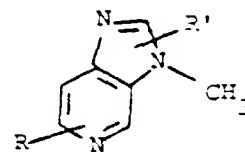
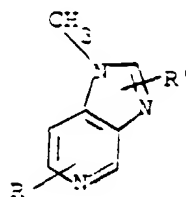
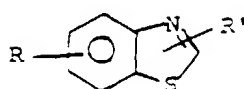
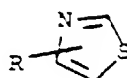
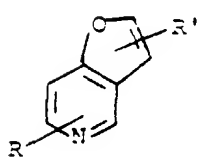
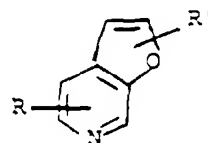
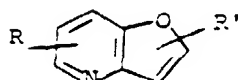
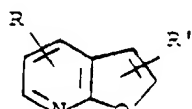
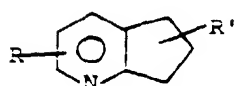
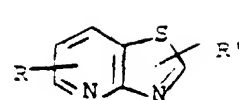
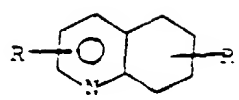
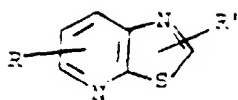
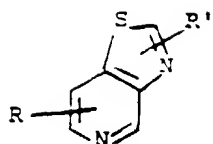
L'invention a pour objet les produits de formule générale (I) :

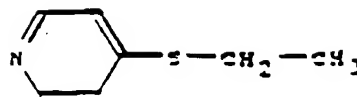
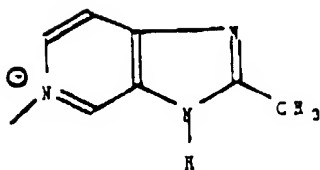
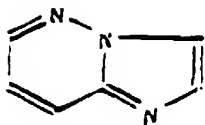


isomère syn, sous forme R ou S ou d'un mélange R, S, formule dans laquelle :

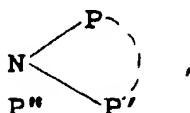
R<sub>1</sub> représente un radical choisi parmi les radicaux suivants :



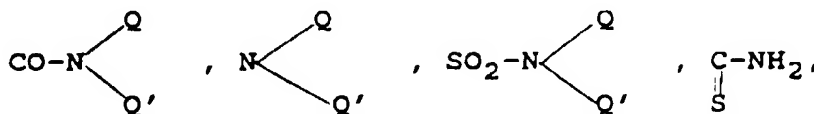




ou



sous forme d'ammonium quaternaire, l'expression sous forme d'ammonium quaternaire indiquant que le radical  $R_1$  est lié avec le groupement  $-\text{CH}=\text{CH}-\text{CH}_2$  par le ou l'un des atomes d'azote qu'il comporte, dans lesquels R et R' identiques ou différents représentent un atome d'hydrogène, un radical alkyle renfermant de 1 à 4 atomes de carbone, un radical alcoxy renfermant de 1 à 4 atomes de carbone, un atome d'halogène, un radical  $\text{CO}_2-\text{Q}$ ,



$\text{NH}-\text{CO}-\text{Q}$ ,  $\text{CN}-\text{CH}_2-\text{CN}$ ,  $\text{CH}_2-\text{SQ}$  dans lesquels Q et Q' identiques ou différents représentent un atome d'hydrogène ou un radical alkyle renfermant de 1 à 4 atomes de carbone, P, P' et P'' identiques ou différents représentent un radical alkyle renfermant au plus 4 atomes de carbone, éventuellement substitué par un des substituants indiqués ci-dessus pour R et R', le symbole } indiquant que P et P' peuvent éventuellement former avec l'atome d'azote auquel ils sont liés, un hétérocycle à 5 ou 6 chaînons,

$R_b$  et  $R_c$ , identiques ou différents représentent un atome d'hydrogène ou un groupement acyle, choisi parmi les radicaux acétyl, propionyl et benzoyl,

A et A' identiques ou différents représentent un atome d'hydrogène, un équivalent de métal alcalin, alcalino-terreux, de magnésium, d'ammonium ou d'une base organique aminée ou A et A' représentent le reste d'un groupement ester facilement clivable ou  $\text{CO}_2\text{A}$  représente  $\text{CO}_2^-$  le trait ondulé signifie que le groupement  $\text{CH}_2\text{R}_1$  peut se trouver dans la position E ou Z ainsi que les sels des produits de formule (I) avec les acides minéraux ou organiques.

Par radical alkyle renfermant de 1 à 4 atomes de carbone, on entend par exemple, méthyle, éthyle, propyle, isopropyle, butyle linéaire ou ramifié.

Lorsque P et P' forment un hétérocycle avec l'atome d'azote auquel ils sont liés, il peut s'agir d'une pyrrolidine, d'une morpholine ou d'une pipéridine.

Lorsque  $R_b$  et/ou  $R_c$  représentent un radical acyle, il peut s'agir des radicaux acétyl, propionyl ou benzoyl. La valeur acyle préférée est la valeur acétyl. La valeur préférée pour  $R_b$  et  $R_c$  est la valeur hydrogène.

Parmi les valeurs de A et de A' on peut citer un équivalent de sodium, de potassium, de lithium, de calcium, de magnésium ou d'ammonium. On peut citer, parmi les bases organiques, la méthylamine, la propylamine, la triméthylamine, la diéthylamine, la triéthylamine, la N,N-diméthyléthanolamine, le tris[(hydroxyméthyl) amino] méthane, l'éthanolamine, la pyridine, la picoline, la dicyclohexylamine, la morpholine, la benzylamine, la procaine, la lysine, l'arginine, l'histidine, la N-méthylglucamine.

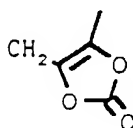
On peut citer entre autres restes de groupements ester facilement clivables que peuvent représenter A et A', les groupements méthoxyméthyle, éthoxyméthyle, isopropylloxyméthyle, alpha-méthoxy éthyle, alpha-éthoxy éthyle, méthylthiométhyle, éthylthiométhyle, isopropylthiométhyle, pivaloyloxyméthyle, acétoxyméthyle, propionylloxyméthyle, butyryloxyméthyle, isobutyryloxyméthyle, valéryloxyméthyle, isovaléryloxyméthyle, tert-butylcarbonyloxyméthyle, hexadécanoyloxyméthyle, propioniloxyéthyle, isovaléryloxyéthyle, 1-acétyloxyéthyle, 1-propioniloxyéthyle, 1-butyryloxyéthyle, 1-tert-butylcarbonyloxyéthyle, 1-acétyloxypropyle, 1-hexadécanoyloxyéthyle, 1-propioniloxypropyle, 1-méthoxycarbonyloxyéthyle, méthoxycarbonyloxyméthyle, 1-acétyloxybutyle, 1-acétyloxyhexyle, 1-acétyloxyheptyle,



phthalidyle, 5,6-diméthoxyphtali dyle, tert-butylcarbonylméthyle, allyle, 2-chloroallyle, méthoxycarbonylméthyle, benzy-  
le ou tert-butyle.

On peut encore citer entre autres restes de groupements esters que peuvent représenter A et A', les groupements  
méthoxyéthoxyméthyle, diméthylaminoéthyle, cyanométhyle, tert-butoxycarbonylméthyle, 2,2-éthylènedioxyéthyle,  
cyanoéthyle, 2,2-diméthoxyéthyle ; 2-chloroéthoxyméthyle, 2-hydroxyéthoxyéthyle, 2,3-époxypropyle, 3-diméthylami-  
no, 2-hydroxypropyle, 2-hydroxyéthyle, 2-méthylaminoéthoxyméthyle, 2-aminoéthoxyméthyle, 3-méthoxy 2,4-thiadia-  
zol-5-yle, 2-tétrahydropyrannyle, 1-méthoxy 1-méthyl éthyle, 2-hydroxy 1-méthyl éthyle, isopropyle ; carbamoylméthyle,  
chlorométhyle, 2-chloroéthyle, acétylméthyle, 2-méthylthioéthyle ou thiocyanatométhyle.

On peut encore citer entre autres restes de groupements esters que peuvent représenter A et A', les groupements  
2-chloro 1-acétyloxyéthyle, 2-bromo 1-acétyloxyéthyle, 2-fluoro 1-acétyloxyéthyle, 2-méthoxy 1-acétyloxyéthyle, 2-mé-  
thyl 1-acétyloxypropyle, 1-méthyl 1-acétyloxyéthyle, 1-méthoxyacétyloxyéthyle, 1-acétylcarbonyloxyéthyle, 1-hy-  
droxyacétyloxyéthyle, 1-formylcarbonyloxyéthyle, 1-(2-thiényle) carbonyloxyéthyle, 1-(2-furyl) carbonyloxyéthyle, 1-  
(5-nitro 2-furyl) carbonyloxyéthyle, 1-(2-pyrrolyl) carbonyloxyéthyle, 1-(propionyloxycarbonyloxy) éthyle, 1-(propyloxy-  
carbonyloxy) éthyle, 1-(isopropyloxycarbonyloxy) éthyle, 1-(méthoxyéthoxycarbonyloxy) éthyle, 1-(allyloxycarbony-  
loxy) éthyle, isopropyloxycarbonyl méthyle, 1-[(2,3-époxy propyl) oxycarbonyloxy] éthyle, 1-[(2-furyl) méthyloxycarbo-  
nyloxy] éthyle, 1-(2-fluoro éthyl) oxycarbonyloxyéthyle, 1-(méthoxycarbonyloxy) propyle, 1-(méthoxycarbonyloxy)  
1-méthyl éthyle, (méthoxycarbonyloxy) chlorométhyle, 1-(méthoxycarbonyloxy) 2-chloroéthyle, 1-(méthoxycarbonyloxy)  
2-méthoxy éthyle, 1-(méthoxycarbonyloxy) allyle, ou un reste :



Les produits de formule (I) peuvent également se présenter sous forme de sels d'acides organiques ou minéraux.

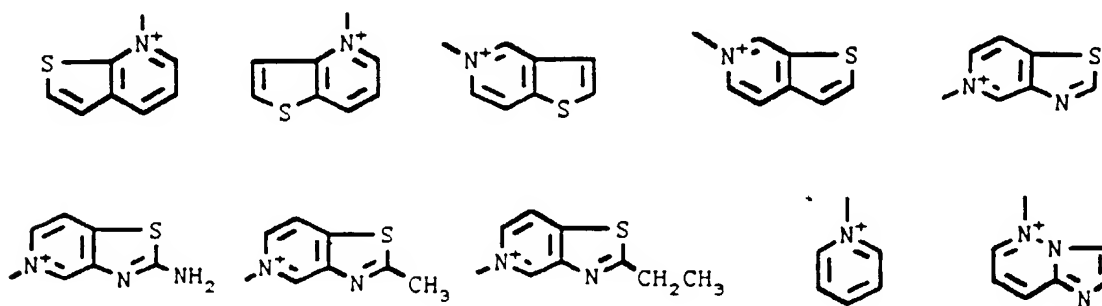
Parmi les acides avec lesquels on peut salifier le ou les groupements amino des produits (I), on peut citer entre  
autres, les acides acétique, trifluoroacétique, maléïque, tartrique, méthanesulfonique, benzènesulfonique, para-toluène  
sulfonique, phosphorique, sulfurique, chlorhydrique, bromhydrique, iodhydrique.

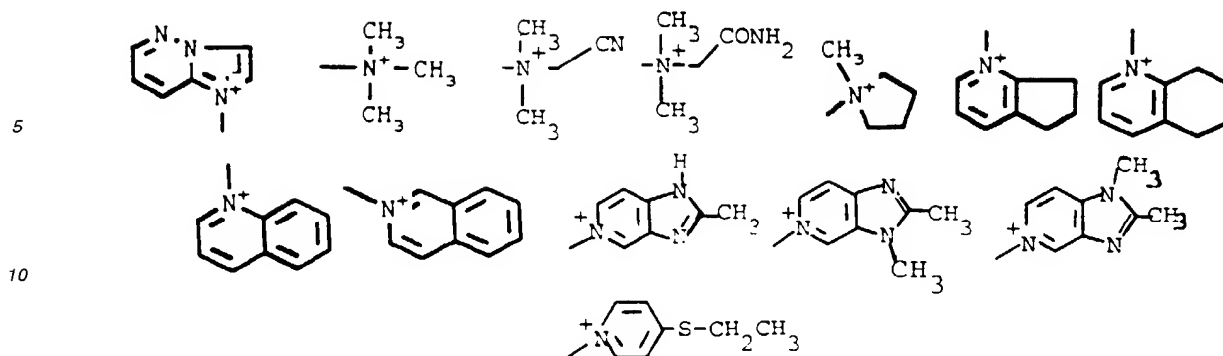
Les produits peuvent également se présenter sous forme de sels internes.

Dans un mode préféré de l'invention, A' représente un atome d'hydrogène ou de sodium, de préférence hydrogène  
et CO<sub>2</sub>A représente CO<sub>2</sub><sup>⊖</sup>.

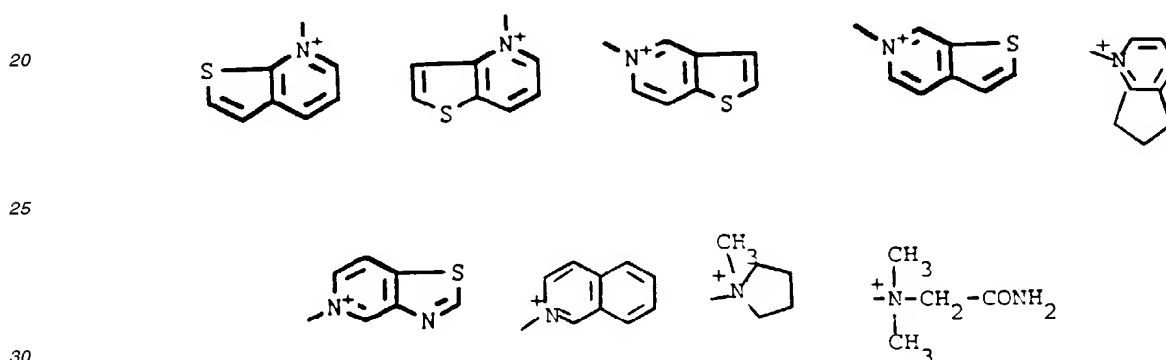
L'expression sous forme d'ammonium quaternaire indique que le radical R<sub>1</sub> est lié par le ou l'un des atomes d'azote  
qu'il comporte.

L'invention a particulièrement pour objet les produits de formule générale (I) telle que définie ci-dessus dans la-  
quelle R<sub>1</sub> est choisi parmi les radicaux :

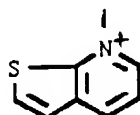




15 L'invention a plus particulièrement pour objet les produits de formule générale (I) telle que définie ci-dessus dans laquelle  $R_1$  est choisi parmi les radicaux



de préférence le radical :



40 L'invention a tout particulièrement pour objet les produits décrits ci-après dans les exemples, à savoir :

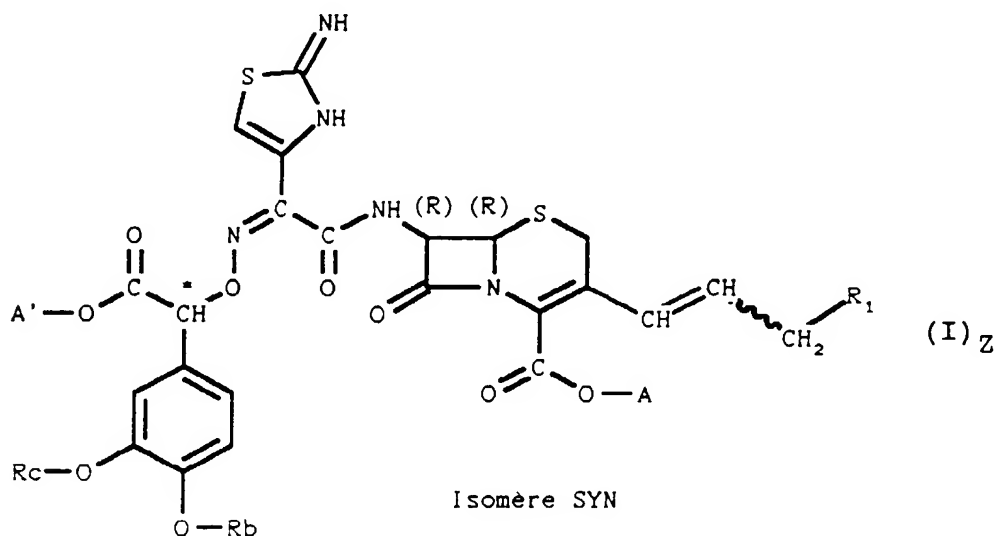
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,1]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c] pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b]pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables et particulièrement sous forme S,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinolinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,

- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) 3-[7-[[[(2-amino4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propèn-1-aminium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables.

Il est entendu que les produits de formule (I) précités peuvent exister :

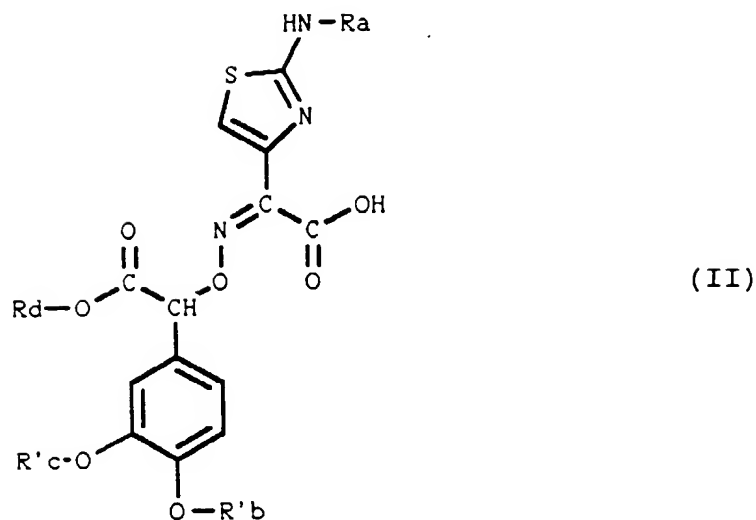
soit sous la forme indiquée par ladite formule (I),

soit sous la forme de produits de formule (I)<sub>Z</sub> :

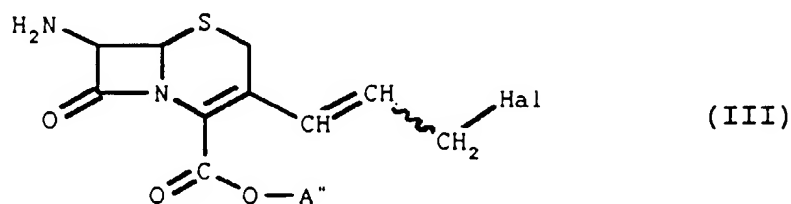


dans laquelle A, A', R<sub>1</sub>, R<sub>b</sub> et R<sub>c</sub> ont la signification précédente.

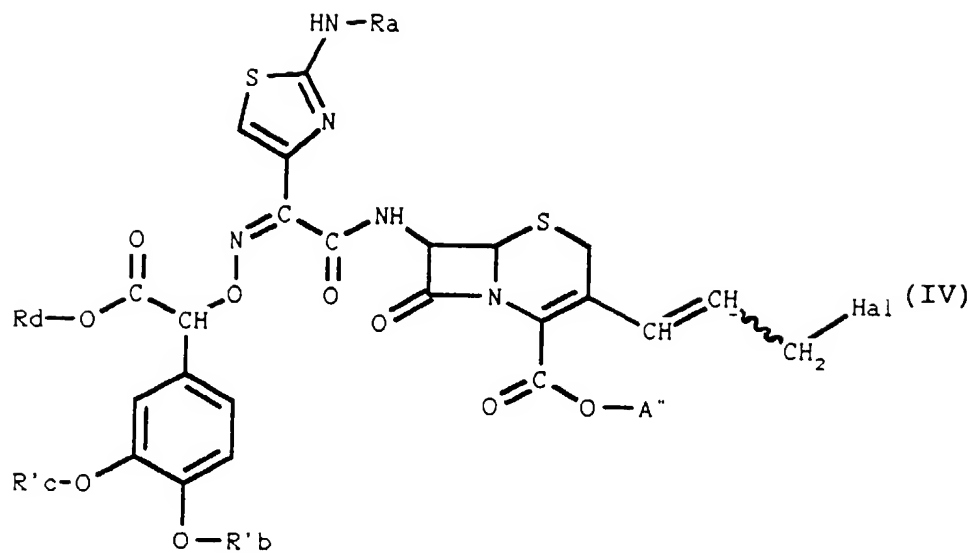
L'invention a également pour objet un procédé de préparation des produits de formule (I) telle que définie ci-dessus, caractérisé en ce que l'on fait agir un produit de formule (II) :



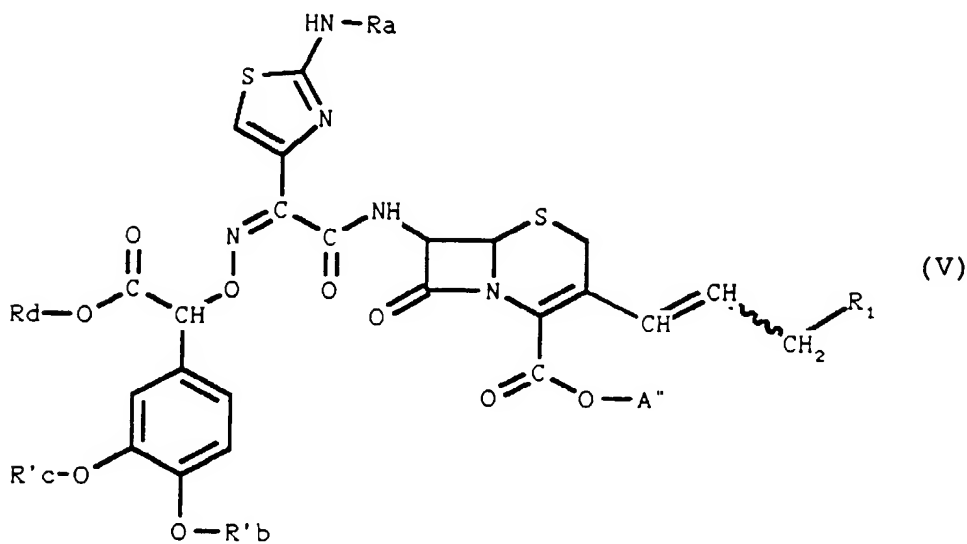
isomère syn, racémique ou optiquement actif ou un dérivé fonctionnel du produit de formule (II), dans laquelle  $R_a$  représente un atome d'hydrogène ou un groupement protecteur du radical amino,  $R'_b$  et  $R'_c$  identiques ou différents représentent un atome d'hydrogène ou un groupement protecteur du radical hydroxyle,  $R_d$  représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable, avec un produit de formule (III) :



dans laquelle Hal représente un atome d'halogène,  $A''$  représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable et le trait ondulé signifie que le groupement  $CH_2Hal$  peut se trouver dans la position E ou Z pour obtenir un produit de formule (IV) :



que l'on fait agir avec un réactif capable d'introduire le radical  $R_1$  pour obtenir un produit de formule (V) :

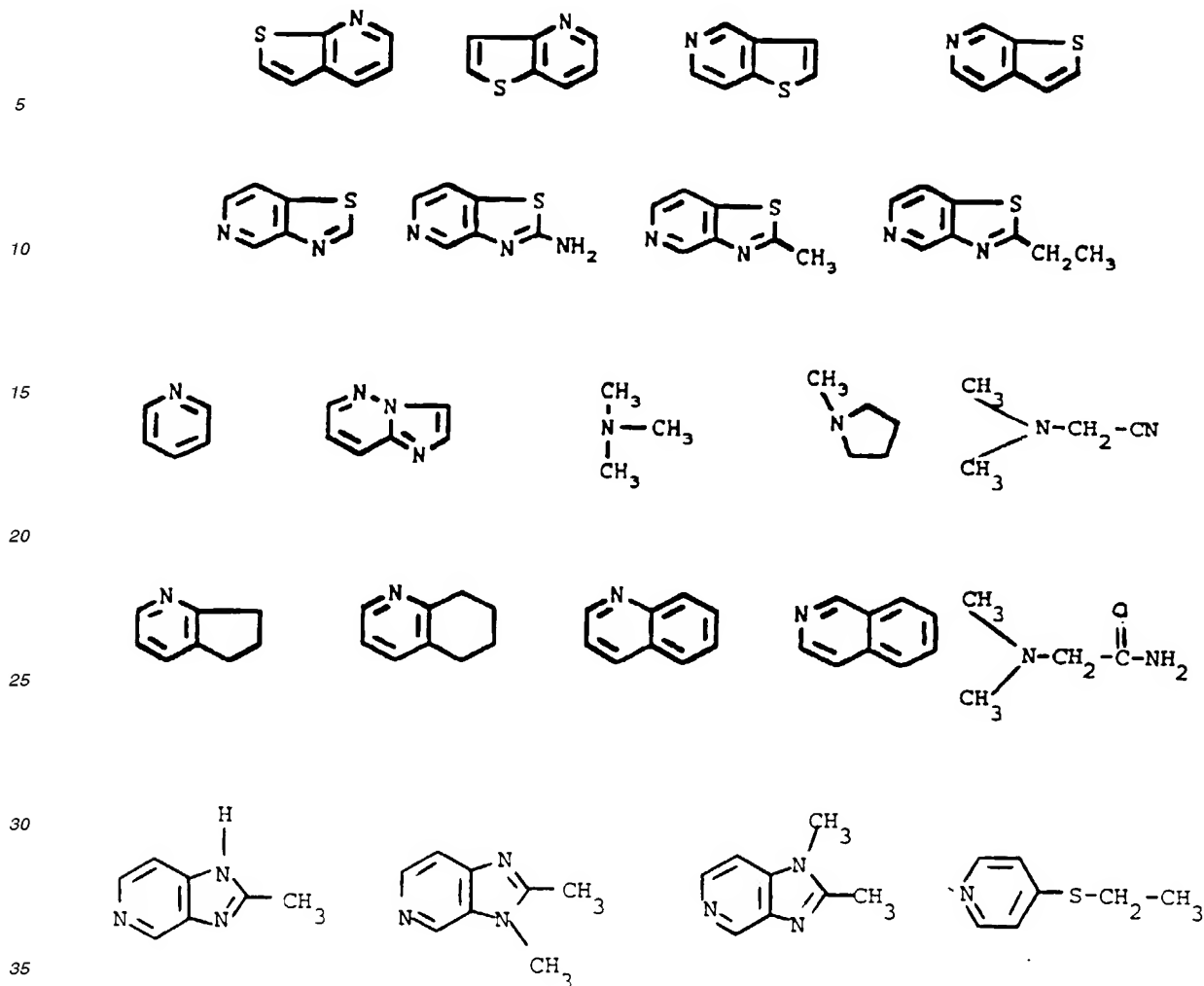


que, si désiré, l'on sépare en ses isomères E ou Z ou transforme les isomères Z en isomères E et produits de formule (V) que, si nécessaire ou si désiré, l'on soumet à une ou plusieurs des réactions suivantes, dans un ordre quelconque :

- a) coupure par hydrolyse ou par action de la thiourée de tout ou partie des groupements esters ou des groupements de protection du radical amino ou des radicaux hydroxyles,
- b) estérification ou salification par une base du ou des radicaux carboxyliques,
- c) salification par un acide du radical amino,
- d) séparation des produits sous forme de mélange R,S en R ou S.

Par réactif capable d'introduire le radical  $R_1$ , on entend un réactif constitué du radical  $R_1$  lui-même, celui-ci n'étant pas sous forme d'ammonium quaternaire ; notamment si l'on veut introduire un radical pyridinium, on opérera avec la pyridine.

Parmi les réactifs préférés, on peut citer ceux répondant aux formules :



En plus des groupements cités ci-dessus, les groupements ester facilement éliminables que peuvent représenter A" et R<sub>d</sub> peuvent être par exemple l'ester formé avec les radicaux butyle, isobutyle, tert-butyle, pentyle, hexyle, acétoxyméthyle, propionyloxyméthyle, butyryloxyméthyle, valéryloxyméthyle, pivaloyloxyméthyle, 2-acétoxyéthyle, 2-propionyloxyéthyle, 2-butyryloxyéthyle.

On peut également citer les radicaux 2-iodoéthyle, 2,2,2-trichloro éthyle, vinyle, allyle, éthynyle, propynyle, benzyle, 4-méthoxybenzyle, 4-nitrobenzyle, phényléthyle, trityle, diphenylméthyle, 3,4-diméthoxyphényle.

On peut également citer les radicaux phényle, 4-chloro phényle, tolyle, tert-butylphényle.

On préfère le radical diphenylméthyle pour R<sub>d</sub> et 4-méthoxybenzyle ou diphenylméthyle pour A".

Le groupement protecteur du radical amino que peut représenter R<sub>a</sub> peut être par exemple un radical alkyle de 1 à 6 atomes de carbone tel que, préférentiellement, tert-butyle ou tert-amyle.

R<sub>a</sub> peut également représenter un groupement acyle aliphatique, aromatique ou hétérocyclique ou un groupe carbamoyle. On peut citer les groupements alcanoyles inférieurs tel que par exemple formyle, acétyle, propionyle, butyryle, isobutyryle, valéryle, isovaléryle, oxalyle, succinyle, pivaloyle.

R<sub>a</sub> peut également représenter un groupe alkoxy ou cycloalkoxycarbonyl inférieur tel que par exemple, méthoxycarbonyl, éthoxycarbonyl, propoxycarbonyl, 1-cyclopropyléthoxycarbonyl, isopropylloxycarbonyl, butylloxycarbonyl, tert-butylloxycarbonyl, pentylloxycarbonyl, hexylloxycarbonyl, un groupe benzoyl, toluoyl, naphthoyl, phthaloyl, mésyl, phénylacétyl, phénylpropionyl, un groupe aralcoxycarbonyl, tel que benzyloxycarbonyl.

Les groupements acyles peuvent être substitués par exemple par un atome de chlore, de brome, d'iode ou de fluor. On peut citer les radicaux chloroacétyl, dichloroacétyl, trichloroacétyl, bromoacétyl ou trifluoroacétyl.

R<sub>a</sub> peut également représenter un groupement aralkyle inférieur tel que benzyle, 4-méthoxybenzyle, phényléthyle, trityle, 3,4-diméthoxybenzyle ou benzhydryle.

$R_a$  peut également représenter un groupe haloalkyle tel que trichloroéthyle.

$R_a$  peut également représenter un groupement chlorobenzoyle, para-nitrobenzoyle, para-tert-butylbenzoyle, phénoxyacétyle, caprylyle, n-décanoyle, acryloyle, trichloroéthoxycarbonyle.

$R_a$  peut également représenter un groupement méthyl carbamoyle, phénylcarbamoyle, naphtylcarbamoyle, ainsi que les thiocarbamoyles correspondants.

On préfère le groupement trityle.

La liste ci-dessus n'est pas limitative, il est évident que d'autres groupements protecteurs des amines, groupements connus en particulier dans la chimie des peptides, peuvent également être utilisés.

Le groupement de protection des radicaux hydroxyles que peuvent représenter  $R'_b$  et  $R'_c$ , peut être choisi dans la liste ci-dessous :

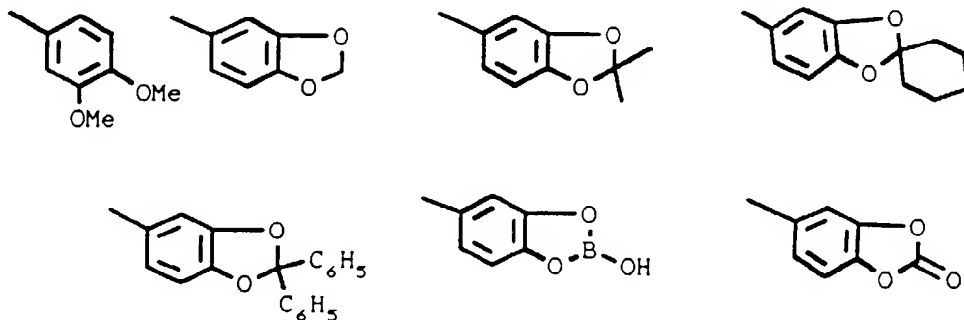
$R'_b$  et  $R'_c$  peuvent représenter un groupe acyle tel que par exemple formyle, acétyle, propionyle, chloroacétyle, bromoacétyle, dichloro-acétyle, trichloroacétyle, trifluoroacétyle, méthoxyacétyle, phénoxyacétyle, benzoyle, benzoylformyle, p-nitrobenzoyle. On peut citer également les groupements éthoxy carbonyle, méthoxycarbonyle, propoxycarbonyle, 2,2,2-trichloro-éthoxycarbonyle, benzyloxycarbonyle, tert-butoxycarbonyle, 1-cyclopropyléthoxycarbonyle, tétrahydropyrannyle, tétrahydrothiopyrannyle, méthoxytétrahydropyrannyle, trityle, benzyle, 4-méthoxybenzyle, benzhydryle, trichloroéthyle, 1-méthyl 1-méthoxyéthyle, phtaloyle.

On peut également citer d'autres acyles tels que butyryle, isobutyryle, valéryle, isovaléryle, oxalyle, succinyle et pivaloyle.

On peut également citer les radicaux phénylacétyle, phénylpropionyle, mésyle, chlorobenzoyle, para-nitrobenzoyle, para-tert-butylbenzoyle, caprylyle, acryloyle, méthylcarbamoyle, phénylcarbamoyle, naphtylcarbamoyle.

On peut également citer les radicaux alkoxy alkoxy méthyle tel que méthoxy éthoxy méthyle.

Les radicaux  $OR'_b$  et  $OR'_c$  peuvent également former avec le radical phényle auquel ils sont liés, les valeurs suivantes :



On préfère le groupement méthoxy éthoxy méthyle pour les substituants  $R'_b$  et  $R'_c$ .

Dans un mode d'exécution du procédé, on fait agir un dérivé fonctionnel du produit de formule (II). Ce dérivé fonctionnel peut être par exemple un halogénure, un anhydride symétrique ou mixte, l'amide, l'azide ou un ester activé.

Comme exemple d'anhydride mixte on peut citer par exemple celui formé avec le chloroformiate d'isobutyle et celui formé avec le chlorure de pivaloyle et les anhydrides mixtes carboxylique-sulfonique formé par exemple avec le chlorure de para-toluène sulfonyle.

Comme exemple d'ester activé, on peut mentionner l'ester formé avec le 2,4-dinitrophénol et celui formé avec l'hydroxybenzothiazole.

Comme exemple d'halogénure, on peut citer le chlorure ou le bromure.

L'anhydride peut être formé in situ par action de carbodiimide N,N'-disubstitué, par exemple le N,N-dicyclohexylcarbodiimide.

La réaction d'acylation est conduite de préférence dans un solvant organique tel que le chlorure de méthylène. On peut cependant utiliser d'autres solvants tels que le tétrahydrofurane, le chloroforme ou le diméthylformamide.

Lorsqu'on utilise un halogénure d'acide et de manière générale lorsqu'une molécule d'acide halohydrique est libérée au cours de la réaction, on réalise la réaction de préférence en présence d'une base telle que la soude, la potasse, les carbonates et carbonates acides de sodium ou de potassium, l'acétate de sodium, la triéthylamine, la pyridine, la morpholine ou la N-méthylmorpholine.

La température de réaction est en général inférieure ou égale à la température ambiante.

On peut également faire agir directement un produit de formule (II) avec un produit de formule (III) en présence d'un carbodiimide telle que le diisopropylcarbodiimide. Un exemple d'une telle préparation est donnée plus loin dans

la partie expérimentale.

L'action des réactifs capable d'introduire le radical  $R_1$  sur le produit de formule (IV) est effectuée dans les conditions suivantes :

Lorsque Hal représente par exemple un atome de chlore, on peut effectuer in situ ou séparément une substitution de l'atome de chlore par un atome d'iode en présence d'iodure de sodium puis ajoute ensuite le réactif désiré, en présence ou non d'un solvant organique tel que l'acétonitrile ou le tétrahydrofurane. Des exemples de telles réactions sont décrits ci-après dans la partie expérimentale.

On peut également faire agir sur le produit de formule (IV) dans lequel Hal représente un atome de chlore, le réactif désiré en présence de tétrafluoroborate d'argent.

Un exemple d'une telle préparation se trouve également dans la partie expérimentale.

L'isomérisation des produits de formule (V) peut être différente de celle des produits de formule (IV) utilisés au départ. Dans le cas où l'on isole l'isomère Z, on peut transformer cet isomère en isomère E selon les méthodes usuelles, notamment par action de l'iode.

Selon les valeurs de  $R_a$ ,  $R'_b$ ,  $R'_c$ ,  $R_d$  et A", les produits de formule (V) peuvent ou non constituer des produits de formule (I).

Les produits de formule (V) constituent des produits de formule (I) lorsque  $R_a$  représente un atome d'hydrogène, lorsque  $R'_b$  et  $R'_c$  ne représentent pas un groupement protecteur du radical hydroxyle que l'on désire éliminer, c'est-à-dire lorsque  $R'_b$  et/ou  $R'_c$  représentent un radical acétyle, propionyle ou benzoyle et lorsque  $R_d$  et A" ne représentent pas, parmi les groupements esters facilement clivables, l'un de ceux que l'on désirerait éliminer.

Dans les autres cas, l'action sur le produit de formule (V) d'un ou plusieurs agents d'hydrolyse, d'hydrogénolyse ou de la thiourée a pour but d'éliminer le radical  $R_a$  lorsque celui-ci représente un radical protecteur du radical amino, d'éliminer les radicaux  $R'_b$  et  $R'_c$  lorsque ceux-ci représentent un groupement protecteur des radicaux hydroxyle et/ou d'éliminer les radicaux  $R_d$  et A" lorsque ceux-ci représentent, parmi les groupements esters facilement clivables l'un de ceux que l'on désire éliminer.

Cependant, il est bien entendu possible d'éliminer  $R_a$ ,  $R'_b$  et  $R'_c$  sans toucher aux substituants  $R_d$  et A" lorsque ceux-ci doivent être conservés. Il en est ainsi par exemple lorsque A" représente un groupement ester que l'on souhaite conserver tel qu'un groupement propionyloxyméthyle.

La nature des réactifs à mettre en jeu dans un tel cas est bien connu de l'homme de métier. Des exemples de telles réactions sont donnés plus loin dans la partie expérimentale.

On trouvera par exemple une description des différentes méthodes d'élimination des différents groupements protecteurs dans la demande de brevet français B.F. 2.499.995.

Etant donné les groupements protecteurs préférés que l'on utilise : trityle pour  $R_a$ , méthoxy éthoxy méthyle pour  $R'_b$  et  $R'_c$ , diphenylméthyle pour  $R_d$  et 4-méthoxybenzyle ou diphenylméthyle pour A", on utilise de préférence l'acide trifluoroacétique sans solvant ou dans un solvant tel que l'anisole ou un mélange de solvants tels que anisole/chlorure de méthylène. On obtient alors un sel avec l'acide trifluoroacétique. On peut revenir à la base libre par action d'une base telle que le carbonate de triéthylamine.

La salification des produits peut être effectuée selon les méthodes usuelles.

La salification peut, par exemple, être obtenue par action, sur un produit sous forme acide ou sur un solvat, par exemple, le solvat éthanolique ou un hydrate de cet acide, d'une base minérale telle que l'hydroxyde de sodium ou de potassium, le carbonate ou le carbonate acide de sodium ou de potassium. On peut également utiliser les sels d'acides minéraux tels que le phosphate trisodique. On peut également faire appel à des sels d'acides organiques.

Comme sels d'acides organiques, on peut mentionner, par exemple, les sels de sodium d'acides carboxyliques aliphatiques, linéaires ou ramifiés, saturés ou insaturés de 1 à 18 et de préférence de 2 à 10 atomes de carbone. Les chaînes aliphatiques de ces acides peuvent être interrompues par un ou plusieurs hétéroatomes tels que l'oxygène ou le soufre ou substituées par des radicaux aryle, comme, par exemple : phényle, thiényl, furyl, par un ou plusieurs radicaux hydroxyles ou par un ou plusieurs atomes d'halogène tels que fluor, chlore ou brome, préférentiellement chlore, par un ou plusieurs radicaux carboxyliques ou alkoxy-carbonyles inférieurs, de préférence méthoxycarbonyl, éthoxycarbonyl ou propyloxycarbonyl, par un ou plusieurs radicaux aryloxy, de préférence phénoxy.

De plus, on peut utiliser comme acides organiques, des acides aromatiques suffisamment solubles comme, par exemple, des acides benzoïques substitués, de préférence par des radicaux alkyles inférieurs.

Comme exemples de tels acides organiques, on peut mentionner :

les acides formique, acétique, acrylique, butyrique, adipique, isobutyrique, n-caproïque, isocaproïque, chloropropioniques, crotonique, phénylacétique, 2-thiénylacétique, 3-thiénylacétique, 4-éthylphénylacétique, glutarique, l'ester monoéthylque de l'acide adipique, les acides hexanoïque, heptanoïque, décanoïque, oléïque, stéarique, palmitique, 3-hydroxypropionique, 3-méthoxypropionique, 3-méthylthiobutyrique, 4-chlorobutyrique, 4-phénylbutyrique, 3-phénoxybutyrique, 4-éthylbenzoïque, 1-propylbenzoïque.

On utilise cependant de préférence comme sels de sodium, l'acétate de sodium, le 2-éthyl hexanoate de sodium ou le diéthyl acétate de sodium.



La salification peut également être obtenue par action d'une base organique comme la triéthylamine, la diéthylamine, la triméthylamine, la propylamine, la N,N-diméthyl éthanolamine, le tris(hydroxyméthyl) amino] méthane, la méthylamine, l'éthanolamine, la pyridine, la picoline, la dicyclohexyl amine, la morpholine et la benzylamine.

Elle peut également être obtenue par action de l'arginine, de la lysine, de la procaine, de l'histidine, de la N-méthyl glucamine.

Cette salification est réalisée de préférence dans un solvant ou un mélange de solvants tels que l'eau, l'éther éthylique, le méthanol, l'éthanol ou l'acétone.

Les sels sont obtenus sous forme amorphe ou cristallisée selon les conditions réactionnelles employées.

Les sels cristallisés sont préparés de préférence en faisant réagir les acides libres avec l'un des sels des acides carboxyliques aliphatiques mentionnés ci-dessus, de préférence, avec l'acétate de sodium.

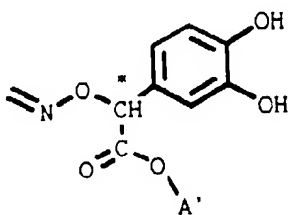
La salification des produits par les acides minéraux ou organiques est effectuée dans les conditions usuelles.

L'estérification éventuelle des produits est effectuée dans les conditions classiques. On opère en général en faisant réagir l'acide de formule (I) ou un dérivé fonctionnel avec un dérivé de formule :



dans laquelle Z représente un radical hydroxyle ou un atome d'halogène tel que le chlore, le brome, l'iode et Re désigne le groupement ester à introduire, groupement dont une liste non exhaustive figure ci-dessus. Dans certains cas, il peut être avantageux d'effectuer une estérification sur un produit dont l'amine et/ou les groupements réactionnels présents sur l'oxymino sont bloqués avant d'enlever le groupement protecteur de l'amine et du groupement réactionnel présents sur l'oxymino.

Les produits de formule (I) comportent plusieurs carbones asymétriques. Dans le noyau cephème, qui comporte deux carbones asymétriques, les deux carbones sont dans la configuration R. Par ailleurs le radical présent sur la fonction oxymino comporte également un carbone asymétrique :



qui peut être sous forme R ou S ou sous forme d'un mélange R,S. La séparation des deux diastéréoisomères peut être effectuée par les moyens connus de l'homme du métier, par exemple par chromatographie.

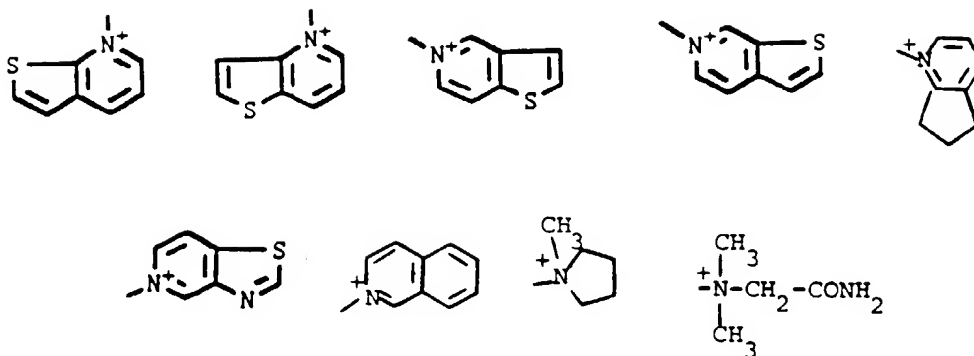
Les produits de formule générale (I) possèdent une très bonne activité antibiotique sur les bactéries gram (+) telles que les staphylocoques, les streptocoques et notamment sur les staphylocoques pénicillino-résistants. Leur efficacité sur les bactéries gram (-) notamment sur les bactéries coliformes, les klebsiella, les salmonella, les proteus et les pseudomonas, est particulièrement remarquable.

Ces propriétés rendent aptes lesdits produits ainsi que leurs sels d'acides pharmaceutiquement acceptables à être utilisés comme médicaments dans le traitement des affections à germes sensibles et notamment dans celui des staphylococcies, telles que septicémies à staphylocoques, staphylococcies malignes de la face ou cutanée, pyodermites, plaies septiques ou suppurantes, anthrax, phlegmons, érysipèles, staphylococcies aiguës primitives ou post grippales, broncho-pneumonies, suppurations pulmonaires.

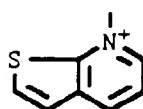
Ces produits peuvent également être utilisés comme médicaments dans le traitement des colibacillooses et infections associées, dans les infections à proteus, à klebsiella et à salmonella et dans d'autres affections provoquées par des bactéries à gram (-).

La présente invention a donc également pour objet, à titre de médicaments et notamment de médicaments antibiotiques, les produits de formule (I) tels que définis ci-dessus ainsi que leurs sels d'acides pharmaceutiquement acceptables.

L'invention a plus particulièrement pour objet à titre de médicaments les produits de formule (I) telle que décrite ci-dessus dans laquelle R<sub>1</sub> est choisi parmi les radicaux :



de préférence le radical :



L'invention a spécialement pour objet, à titre de médicaments et notamment de médicaments antibiotiques, les produits décrits ci-après dans les exemples, à savoir :

- le [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c]pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables, pharmaceutiquement acceptables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b]pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables et particulièrement sous forme S, pharmaceutiquement acceptables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinoléinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables, pharmaceutiquement acceptables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables, pharmaceutiquement acceptables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables, pharmaceutiquement acceptables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) 3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propèn-1-aminium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables, pharmaceutiquement acceptables.

L'invention s'étend aux compositions pharmaceutiques renfermant, comme principe actif, au moins un des médicaments définis ci-dessus.

Ces compositions peuvent être administrées par voie buccale, rectale, parentérale, notamment intramusculaire ou par voie locale en application topique sur la peau et les muqueuses.

Les produits de formule (I) et notamment ceux dans laquelle A représente un ester clivable peuvent être administrés par voie orale.

Les compositions selon l'invention peuvent être solides ou liquides et se présenter sous les formes pharmaceutiques couramment utilisées en médecine humaine comme par exemple, les comprimés simples ou dragéifiés, les gélules, les granulés, les suppositoires, les préparations injectables, les pommades, les crèmes, les gels ; elles sont préparées selon les méthodes usuelles. Le ou les principes actifs peuvent y être incorporés à des excipients habituellement employés dans ces compositions pharmaceutiques, tels que le talc, la gomme arabique, le lactose, l'amidon, le stéarate de magnésium, le beurre de cacao, les véhicules aqueux ou non, les corps gras d'origine animale ou végétale, les dérivés paraffiniques, les glycols, les divers agents mouillants, dispersants ou émulsifiants, les conservateurs.

Ces compositions peuvent notamment se présenter sous forme d'une poudre destinée à être dissoute extemporanément dans un véhicule approprié, par exemple, de l'eau stérile apyrogène.

La dose administrée est variable selon l'affection traitée, le sujet en cause, la voie d'administration et le produit considéré. Elle peut être, par exemple, comprise entre 0,250 g et 4 g par jour, par voie orale chez l'homme, avec le produit décrit à l'exemple 1 ou encore comprise entre 0,500 g et 1 g trois fois par jour par voie intramusculaire.

Les produits de formule (I) peuvent également être utilisés comme désinfectants des instruments chirurgicaux.

L'invention a enfin pour objet, à titre de produits industriels nouveaux et notamment à titre de produits intermédiaires nécessaires à la préparation des produits de formule (I) telle que définie ci-dessus, les produits de formule (IV) et les produits de formule (V) dans laquelle  $R_a$  représente un groupement protecteur du radical amino, les formules (IV) et (V) étant telles que définies ci-dessus.

Les produits de formule (II) sont connus dans la littérature, notamment dans les demandes de brevets européens EP 0.238.061 ou EP 0.266.060 ou peuvent être préparés selon les méthodes usuelles ;

Les produits de formule (III) sont également connus dans la littérature, notamment dans les demandes de brevets britanniques GB 2.134.522 ou allemandes DE 3512225.

Les exemples suivants illustrent l'invention sous toutefois la limiter.

**EXEMPLE 1 : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[1,2,0]oct-2-en-3-yl] 2-propényl]thiéno [2,3-b]pyridinium trifluoroacétate tétrafluoroborate**

**STADE A : [6R-[3(E), 6alpha, 7bêta(Z)]] diphénylméthyl 7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-ène-2-carboxylate.**

On ajoute 0,372 cm<sup>3</sup> de disopropylcarbodiimide dans 1 cm<sup>3</sup> de chlorure de méthylène à un mélange de 1,876 g d'acide [[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] (diphényl méthoxy carbonyl) méthoxy] imino] [2-(triphényl méthyl amino) 4-thiazolyl] acétique isomère syn, décrit dans le brevet européen EP 238061, 0,955 g de diphénylméthyl 7-amino 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-ène-2-carboxylate décrit dans le brevet allemand DE 35 12 225 et 200 cm<sup>3</sup> de chlorure de méthylène séché.

On agite 45 minutes puis évapore le solvant sous pression réduite et chromatographie sur silice (éluant : chlorure de méthylène 87,5 - acétate d'éthyle 12,5).

On obtient 2,1 g de produit jaune ( $R_f = 0,42$  en chromatographie sur couche mince, éluant : chlorure de méthylène-acétate d'éthyle (8-2)).

Infra-rouge

= C-NH	3402 cm <sup>-1</sup>
	1792 cm <sup>-1</sup> bêta lactame
>= O	1731 cm <sup>-1</sup> ester
	1683 cm <sup>-1</sup> amide secondaire
C=C	1594 cm <sup>-1</sup>
+	1584 cm <sup>-1</sup>
Aromatique	1525 cm <sup>-1</sup>
+	1517 cm <sup>-1</sup>
Amide secondaire	1396 cm <sup>-1</sup>

## Ultra-violet

1) Dans EtOH + 1 cm<sup>3</sup> CHCl<sub>2</sub>

5	infl 217 nm	epsilon = 74300
	infl 238 nm	epsilon = 35500
	infl 271 nm	epsilon = 20800
	infl 296 nm	epsilon = 16400

10 2) Dans EtOH + HCl 0,1 N

	infl 217 nm	epsilon = 76400
	infl 239 nm	epsilon = 28800
	max 283 nm	epsilon = 26200

15 infl 271, 291 et 305 nm.

20 STADE B : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[[1-[3,4-bis(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b]pyridinium tétrafluoroborate

On traite aux ultrasons un mélange de 55,9 mg de tétrafluoroborate d'argent, 38,8 mg de thiéno[2,3-b]pyridine et 5 cm<sup>3</sup> de chlorure de méthylène puis ajoute 136 mg de produit obtenu au stade A légèrement dilué dans le chlorure de méthylène et agite pendant 1 h 15.

25 On filtre, évapore, reprend le résidu par de l'éther, on obtient un solide que l'on lave par 3 fois 3 cm<sup>3</sup> d'éther et obtient 207 mg de produit que l'on purifie par chromatographie sur silice (éluant : chlorure de méthylène-méthanol). On évapore les fractions et obtient 62 mg de produit. Rf = 0,28 en chromatographie sur couche mince (éluant : chlorure de méthylène-méthanol (9:1)).

30 Ultra-violet

1) Dans EtOH

	max 238 nm	epsilon = 368
35	infl 287 nm	epsilon = 168
	max 300 nm	epsilon = 184

2) Dans EtOH, HCl 0,1 N

40	infl 236 nm	epsilon = 333
	max 293 nm	epsilon = 209

45 STADE C : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b]pyridinium trifluoroacétate tétrafluoroborate

On mélange à 0°C deux solutions :

- 50 a) 0,180 g de produit obtenu au stade B, 4,3 cm<sup>3</sup> de chlorure de méthylène et 0,86 cm<sup>3</sup> d'anisole,  
b) 8,6 cm<sup>3</sup> d'acide trifluoroacétique et 4,3 cm<sup>3</sup> de chlorure de méthylène, et agite pendant une heure à 0°C.

On évapore, reprend à l'éther le produit obtenu qui se concrète. On filtre, lave à l'éther et obtient 100,6 mg de produit que l'on place dans 3,3 cm<sup>3</sup> de solution d'acide trifluoroacétique à 10 % d'anisole.

55 On agite une heure à 0°C, évapore puis précipite le produit à l'éther. On filtre, rince et obtient 87,9 mg de produit attendu.

**EXEMPLE 2 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[1,2,0]oct-2-en-3-yl] 2-propényl] thiéno [2,3-b]pyridinium sous forme de sel interne

On élue sur colonne de silice RP 18 par un mélange  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  (50-50) un mélange de 89,4 mg de produit obtenu, comme à l'exemple 1, 2,84  $\text{cm}^3$  d'acétonitrile et 2,84  $\text{cm}^3$  de solution de carbonate de triéthylamine à 0,1 N.

On lyophilise les fractions intéressantes et obtient 50,8 mg de produit attendu.

Infra-rouge (Nujol)

Bêta lactame	1770 $\text{cm}^{-1}$
Autres C = O	1675 $\text{cm}^{-1}$ $\approx 1598 \text{ cm}^{-1}$

Ultra-violet, dans EtOH, HCl 0,1 N

max 240 nm	epsilon = 28600
max 290 nm	epsilon = 24000

**EXEMPLE 3 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c]-c]pyridinium trifluoroacétate iodure

**STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] diphénylméthyl 7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-iodo 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-ène-2-carboxylate.

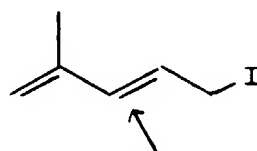
On agite pendant 2 heures à température ambiante un mélange de 650 mg de produit obtenu au stade A de l'exemple 1, 19,1  $\text{cm}^3$  d'acétone et 216,3 mg d'iodure de sodium, évapore le solvant puis reprend le résidu par 26,5  $\text{cm}^3$  d'acétate d'éthyle.

On lave la solution par 3 fois 15  $\text{cm}^3$  de thiosulfate de sodium puis par 2 fois 15  $\text{cm}^3$  d'eau.

On sèche sur sulfate de magnésium, filtre et rince, évapore, reprend par un mélange chlorure de méthylène-acétate d'éthyle (7-3), ajoute 5,3 g de silice, agite pendant 5 minutes puis filtre et rince.

On obtient 445 mg de produit après évaporation ( $R_f = 0,54$  sur chromatographie sur couche mince, éluant chlorure de méthylène-acétate d'éthyle (7-3)).

RMN dans  $\text{CDCl}_3$



ppm : 6,09 (dm J = 16)  
6,12 (dm J = 16)

**STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c]pyridinium iodure

On agite pendant 5 heures un mélange de 445,2 mg de produit obtenu au stade A dans la plus petite quantité possible de diméthylsulfoxyde et 48,2 mg de thiazolo[4,5-c]pyridine puis élimine le solvant sous pression réduite.

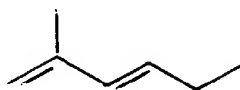
On lave le résidu visqueux par 3 fois 7  $\text{cm}^3$  d'éther. On obtient 374,6 mg d'un solide que l'on purifie sur silice (éluant : chlorure de méthylène-méthanol (92-8)).

On obtient 24 mg de produit ayant l'isomère Z, 21,2 mg de mélange E+Z et 154,3 mg de produit ayant l'isomère

E (R<sub>f</sub> = 0,18 sur chromatographie sur couche mince, éluant : chlorure de méthylène-méthanol (9-1)).

RMN (CDCl<sub>3</sub>)

5



10

6,50 ppm 1H

15

**STADE C** : [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c] pyridinium trifluoroacétate iodure

On mélange à 0°C et agite pendant une heure les deux solutions suivantes :

20

- a) 238,6 mg de produit obtenu au stade B, 5,7 cm<sup>3</sup> de chlorure de méthylène et 1,14 cm<sup>3</sup> d'anisole et
- b) 11,4 cm<sup>3</sup> d'acide trifluoroacétique dans 5,7 cm<sup>3</sup> de chlorure de méthylène.

25

On évapore les solvants puis précipite le produit à l'éther. On filtre, lave et obtient 0,124 g de produit que l'on mélange à 4,14 cm<sup>3</sup> d'acide trifluoroacétique et 0,46 cm<sup>3</sup> d'anisole. On agite 40 minutes en maintenant la température à 0°C. On évapore puis précipite le produit avec de l'éther. On filtre puis rince à l'éther. On sèche et obtient 95,8 mg de produit attendu.

30

**EXEMPLE 4** : [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c]pyridinium sous forme de sel interne

On passe sur colonne de silice RP18, une solution de 95 mg de produit obtenu à l'exemple 3, 3,6 cm<sup>3</sup> d'acétonitrile et 3,8 cm<sup>3</sup> de carbonate de triéthylamine. On élue la colonne par un mélange acétonitrile-eau (50-50). On lyophilise les fractions intéressantes et obtient 63,8 mg de produit attendu.

35

Ultra-violet, dans EtOH, HCl 0,1N

max 225 nm      epsilon = 38500  
max 286 nm      epsilon = 23500

40

infl 274, 300 et 356 nm

Infra-rouge (Nujol)

45

$\text{>C=O}$	1770 cm <sup>-1</sup> Béta lactame
	1676 cm <sup>-1</sup> complexe
Région aromatique	1626 cm <sup>-1</sup>
COO <sup>-</sup>	1596 cm <sup>-1</sup>
Amide secondaire	1536 cm <sup>-1</sup>

50

**EXEMPLE 5** : [6R-[3(E) 6alpha, 7bêta (Z)]] 4-[3-[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo [4,2,0] oct-2-èn-3-yl] 2(E)-propényl] thiéno[3,2-b]pyridinium trifluoroacétate tétrafluoroborate.

55

**STADE A** : [6R-[3(E) 6alpha, 7bêta (Z)]] 4-[3-[7-[[[3,4-bis [(2-méthoxyéthoxy) méthoxy] phényl] 2-[(diphényl méthoxy) 2-oxoéthoxy] imino] [2-(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl 8-oxo 5-thia 1-azabicyclo [4,2,0] oct-2-èn-3-yl] 2(E)-propényl] thiéno [3,2-b]pyridinium tétrafluoroborate.

On opère comme au stade B de l'exemple 1 en utilisant au départ 1,2 g de produit préparé comme indiqué au

stade A de l'exemple 1, 346 mg de fluoroborate d'argent dans 44 cm<sup>3</sup> de chlorure de méthylène et 0,24 cm<sup>3</sup> de thiéno [3,2-b]pyridine et obtient après chromatographie sur silice (éluant : chlorure de méthylène-méthanol 92-8 puis 96-4) 337 mg de produit attendu.

5 RMN (CDCl<sub>3</sub> 300 Hz)

-CH=CH-CH<sub>2</sub>- : 6,23 (dm, J=16) delta E  
 -CH=CH-CH<sub>2</sub>- : 5,44 (m)  
 les CH du thiényl : 7,67 (d, dédoublé) 8,25 (d, dédoublé)  
 10 les CH de la pyridine : 7,76 (m), 8,74 (d, dédoublé), 8,93 (d, dédoublé)

STADE B : [6R-[3(E) 6alpha, 7bêta (Z)]] 4-[3-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo [4,2,0]oct-2-èn-3-yl] 2(E)-propényl] thiéno[3,2-b]pyridinium trifluoroacétate tétrafluoroborate.

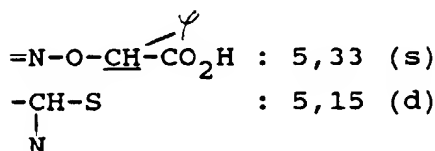
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On opère comme au stade C de l'exemple 1 en utilisant au départ 316,1 mg de produit obtenu ci-dessus au stade A, 1,51 cm<sup>3</sup> d'anisole dans 7,5 cm<sup>3</sup> de chlorure de méthylène et 13,7 cm<sup>3</sup> d'acide trifluoroacétique dans 7,5 cm<sup>3</sup> de chlorure de méthylène. On obtient 183 mg de produit auquel on ajoute de nouveau 6,3 cm<sup>3</sup> d'acide trifluoroacétique à 10% d'anisole et poursuit l'agitation à 0°C pendant 1 heure. On évapore le solvant, reprend le résidu à l'éther, filtre le précipité, le lave à l'éther et le sèche sous pression réduite. On recueille 124,1 mg de produit attendu.

20

RMN (DMSO)

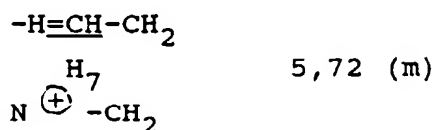
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30

S-CH<sub>2</sub>- : 3,49 (m) partiellement masqué  
 -CH=CH-CH<sub>2</sub>- : 6,33 (dt, J=5 et 8) delta E

35



40

phényl  
 H<sub>5</sub> thiazole 6,57 à 7,07  
 H mobile

45

H<sub>6</sub>', H<sub>3</sub>', H<sub>2</sub>', H<sub>7</sub>', H<sub>5</sub>' du thiénoypyridine : 8,04 à 9,36

50

EXEMPLE 6 : [6R-[3(E) 6alpha, 7bêta (Z)]] 4-[3-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo [4,2,0]oct-2-èn-3-yl] 2(E)-propényl] thiéno[3,2-b]pyridinium trifluoroacétate tétrafluoroacétate.

STADE A : [6R-[3(E), 6alpha, 7bêta(Z)]] diphénylméthyl 7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-iodo 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-ène-2-carboxylate.

55

On opère comme au stade A de l'exemple 3 en utilisant 3 g de produit chloré obtenu au stade A de l'exemple 1 dans 100 cm<sup>3</sup> d'acétone et 1,0 g d'iodure de sodium. On obtient 3,3 g de dérivé iodé identique à celui obtenu à l'exemple

3 utilisé tel quel pour le stade suivant.

**STADE B** : [6R-[3(E), 6alpha, 7bêta(Z)]] 4-[3-[7-[[[1-[3,4-bis(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thieno [3,2-b]pyridinium iodure.

On opère comme au stade B de l'exemple 3 en utilisant 3,3 g du dérivé iodé préparé au stade A, 1,5 cm<sup>3</sup> de thiéno [2,3-b]pyridine et en remplaçant le diméthylsulfoxyde par du chlorure de méthylène. On obtient 1,08 g de produit attendu.

RMN

-CH=CH-CH<sub>2</sub>-N<sup>+</sup> : 5,69 à 5,84 (m) 3H (+ H<sub>7</sub>)

-CH=CH-CH<sub>2</sub>-N<sup>+</sup> : 6,33 (dt), 6,46 (dt)

H du thiénopyridine : 7,83 à 9,72

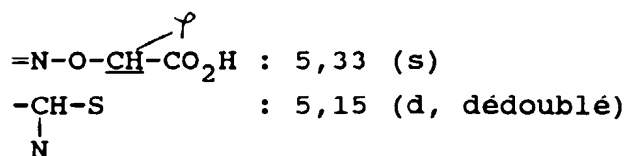
**STADE C** : [6R-[3(E) 6alpha, 7bêta (Z)]] 4-[3-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo [4,2,0]oct-2-èn-3-yl] 2(E)-propényl] thiéno[3,2-b]pyridinium trifluoroacétate tétrafluoroacétate.

On mélange à 0°C et agite pendant une heure les 2 solutions suivantes :

a) 55 cm<sup>3</sup> d'acide trifluoroacétique, 5,5 cm<sup>3</sup> d'anisole et 25 cm<sup>3</sup> de chlorure de méthylène,

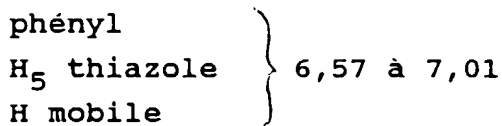
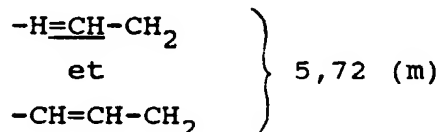
b) 1,19 g de produit obtenu comme au stade B dans 20 cm<sup>3</sup> de chlorure de méthylène et poursuit la synthèse comme indiqué au stade C de l'exemple 3. On obtient 0,62 g de produit attendu.

RMN (DMSO 400 Hz)



S-CH<sub>2</sub>- : 3,49 (m) partiellement masqué

-CH=CH-CH<sub>2</sub>- : 6,33 (dt, J=16 et 8) delta E



H du thiénopyridine : 8,04 à 9,36



**EXEMPLE 7 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] pyridinium trifluoroacétate iodhydrate.

5 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] pyridinium iodure.

10 On opère comme au stade B de l'exemple 6 au départ de 1,47 g de dérivé iodé obtenu comme indiqué au stade A de l'exemple 3 et 480 microlitres de pyridine. On obtient 0,640 g de produit attendu.

RMN (CDCl<sub>3</sub> 400 MHz)

15 -CH=CH-CH<sub>2</sub>-N<sup>⊕</sup> : 5,15 à 5,50  
 CH=CH-CH<sub>2</sub>-N<sup>⊕</sup> : 6,55 (dt, dédoublé) delta E  
 H<sub>2</sub> et H<sub>6</sub> de la pyridine : 9,10 (m)  
 H<sub>3</sub> et H<sub>5</sub> de la pyridine : 7,87 (m)  
 H<sub>4</sub> de la pyridine : 8,27 (t, dédoublé)

20 **STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] pyridinium trifluoroacétate iodhydrate.

25 On opère comme au stade C de l'exemple 6 en utilisant 0,638 g de dérivé obtenu au stade A précédent et obtient 0,314 g de produit attendu.

RMN

30 
$$=N-O-\text{CH}-CO_2H : 5,32 \text{ (s)}$$

35 H<sub>6</sub> : 5,14 (d) et 5,17 (d)  
 H<sub>7</sub> : 5,77 (m)  
 H<sub>5</sub> thiazole : 6,87 (sl)  
 C-NH-CH : 9,55 (d) et 9,62 (d)  
 phényle : 6,65 à 6,80  
 -CH=CH-CH<sub>2</sub> : 7,01 (d, dédoublé)  
 40 -CH=CH-CH<sub>2</sub> : 6,30 (dt) delta E  
 -CH=CH-CH<sub>2</sub> : ≈ 5,41  
 H en 2 et 6 de la pyridine : 9,05 (d)  
 H en 3 et 5 de la pyridine : ≈ 8,13 (d)  
 H en 4 de la pyridine : 8,64 (t)

45 **EXEMPLE 8 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 6-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-c]pyridinium trifluoroacétate iodhydrate.

50 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 6-[3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-c]pyridinium iodure.

55 On opère comme au stade B de l'exemple 6 au départ de 2,08 g de dérivé iodé préparé comme indiqué au stade A de l'exemple 3 et 1 g de thiéno[2,3-c]pyridine. On obtient 0,98 g de produit attendu.

## RMN

## 1) Dans EtOH :

5	Infl. 220 nm	epsilon = 87500
	max. 239 nm	epsilon = 57000
	Infl. 274 nm	epsilon = 25500
	max. 306 nm	epsilon = 27000

## 1) Dans EtOH/HCl 0,1N :

	Infl. 220 nm	epsilon = 87800
	Infl. 236 nm	epsilon = 53600
	max. 284 nm	epsilon = 32600
15	max. 293 nm	epsilon = 32500
	Infl. 320 nm	epsilon = 24000

STADE B : [6R-[3(E), 6alpha, 7bêta(Z)]] 6-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-c]pyridinium trifluoroacétate iodhydrate.

On opère comme au stade C de l'exemple 6 en utilisant 0,966 g de dérivé iodé obtenu au stade A précédent et obtient 0,487 g de produit attendu.

## RMN



	H <sub>7</sub> :	5,78 (m)
	H <sub>5</sub> thiazole :	6,86 (sl)
	phényle :	6,65 à 6,80
35	H <sub>6</sub> , H <sub>7</sub> thiénoypyridine :	7,94 (d), 8,81 (d)
	H <sub>4</sub> , H <sub>5</sub> thiénoypyridine :	8,53 (d), 8,78 (d)
	H <sub>2</sub> thiénoypyridine :	9,91 (s)
	-CH=CH-CH <sub>2</sub> :	7,08 (dl, J=15,5)
	-CH=CH-CH <sub>2</sub> :	6,35 (m) delta E
40	-CH-CH-CH <sub>2</sub> :	5,47 (d)

**EXEMPLE 9 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium trifluoroacétate iodure.

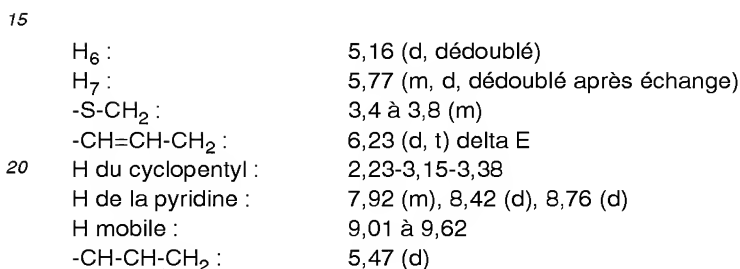
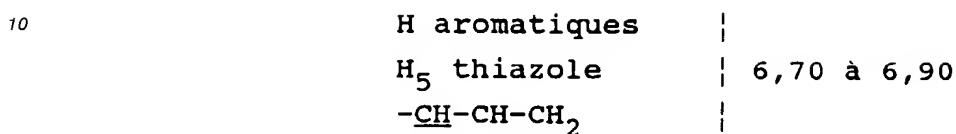
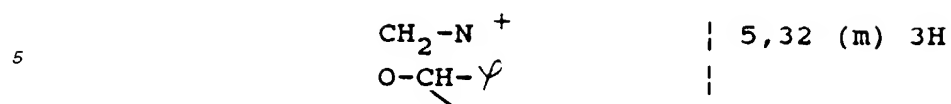
STADE A : [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium iodure

On opère comme au stade B de l'exemple 6 au départ de 1,33 g de dérivé iodé préparé comme au stade A de l'exemple 3 et 0,585 cm<sup>3</sup> de cyclopentyl pyridine. On obtient 1,07 g de produit attendu.

STADE B : [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium trifluoroacétate iodure.

On opère comme au stade C de l'exemple 6 en utilisant 1,053 g du produit obtenu au stade A et obtient le produit attendu.

RMN (DMSO 300 MHz)



25 **EXEMPLE 10 : [6R-[3(E), 6alpha, 7bêta(Z)]] 2-amino 5-[3-[7-[[2-amino4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo [4,5-c]pyridinium trifluoroacétate iodure**

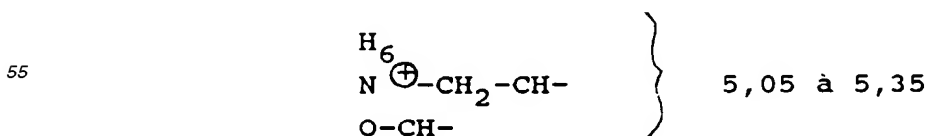
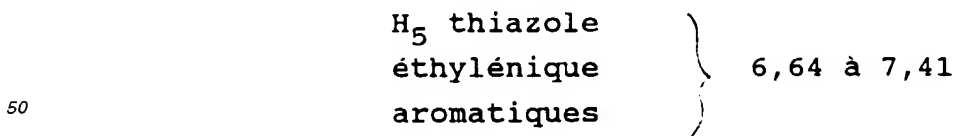
30 **STADE A : [6R-[3(E), 6alpha, 7bêta(Z)]] 2-amino 5-[3-[7-[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(diphénylméthoxy) carbonyl] 8-oxo 5-thia 1-azabicyclo [4,2,0] oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c]pyridinium iodure.**

35 On opère comme au stade B de l'exemple 6 au départ du dérivé iodé préparé comme au stade A de l'exemple 3 (à partir de 272 mg de dérivé chloré et 90 mg d'iodure de sodium) et de 30 mg d'amino thiazolo pyridine. On obtient 42 mg de produit attendu.

40 **STADE B : [6R-[3(E), 6alpha, 7bêta(Z)]] 2-amino 5-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c]pyridinium trifluoroacétate iodure.**

On opère comme au stade C de l'exemple 3 en utilisant 130 mg du produit obtenu comme au stade A et obtient 11,5 mg de produit attendu.

RMN (DMSO 400 MHz)



H<sub>7</sub> : 5,67 (m), 5,76 (m)  
 -CH=CH-CH<sub>2</sub>- : 6,29  
 H<sub>6</sub>, H<sub>7</sub> de la thiazolo pyridine : 8,42 (d), 8,49 (d)  
 H<sub>2</sub> de la thiazolo pyridine : 8,99 (sl)

protons mobiles

| 8,67  
 | 9 (m)  
 | 9,54 (m)  
 | 10,15

**EXEMPLE 11 : [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno [3,2-c] -c]pyridinium trifluoroacétate iodhydrate.**

**STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] p-méthoxybenzyl 7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-(di-phénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl 2-carboxylate.

On refroidit à 0°C une suspension comprenant 3,75 g d'acide [[(3,4-bis [(2-méthoxy éthoxy) méthoxy] phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétique isomère syn, décrit dans le brevet européen EP 238061 et 1,81 g de méthoxybenzyl 7-amino 3-(3-chloropropényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-2-carboxylate (préparé comme indiqué dans le brevet européen EP 0 333 154 dans du chlorure de méthylène, et ajoute 0,920 g de chlorhydrate de N-(diméthylaminopropyl) N'-éthyl carbodiimide. On maintient la solution obtenue à 0°C sous agitation pendant 30 minutes. On lave la phase organique avec une solution aqueuse de chlorure de sodium, sèche et élimine les solvants. Après chromatographie du résidu sur silice (éluant : chlorure de méthylène-éther 85-15) et concrétion dans l'éther isopropylique, on obtient 4,546 g de produit attendu.

RMN (CDCl<sub>3</sub> 400 MHz)

CO<sub>2</sub>-CH<sub>2</sub>-φ : 5,10 à 5,32  
 φ-O-CH<sub>3</sub> : 3,80

**STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] p-méthoxybenzyl 7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-(di-phénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-iodo 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl 2-carboxylate.

On agite pendant 1 heure à température ambiante un mélange de produit obtenu au stade A, 10 cm<sup>3</sup> d'acétone et 341 mg d'iodure de sodium et environ 10 mg d'iode, évapore le solvant puis reprend le résidu par 80 cm<sup>3</sup> de chlorure de méthylène. On lave la phase organique avec une solution aqueuse de thiosulfate de sodium puis à l'eau. On sèche, élimine les solvants, chromatographie sur silice (éluant : chlorure de méthylène-acétate d'éthyle 8-2) et obtient 853 mg de produit attendu.

RMN (CDCl<sub>3</sub> 300MHz)

-CH=CH-CH<sub>2</sub>  
 aromatiques  
 CH=C } 6,9 à 7,35

-CH=CH-CH<sub>2</sub> : 6,13 (d,t J=15 et 8) delta E  
 -CH=CH-CH<sub>2</sub> : 4,0 (d)

**STADE C** : [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxy benzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno [3,2-c]pyridinium iodure.

5 On dissout 2,48 g de dérivé iodé dans 10 cm<sup>3</sup> de chlorure de méthylène et ajoute 1,2 g de thiéno[3,2-c]pyridine en solution dans 2 cm<sup>3</sup> de chlorure de méthylène et triture pendant 1 heure à température ambiante. On ajoute 70 cm<sup>3</sup> d'éther, filtre le précipité, le lave à l'éther, le chromatographie sur silice (éluant : chlorure de méthylène-méthanol 95-5) et obtient 1,117 g de produit attendu.

10 **STADE D** : [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[3,2-c]pyridinium trifluoroacétate iodhydrate.

15 On opère comme au stade C de l'exemple 6 en utilisant 1,117 g du produit obtenu au stade C et obtient 0,618 g de produit attendu.

RMN (DMSO 300 MHz)

20 
$$\text{=N-O-}\underline{\text{CH}}\text{-CO}_2\text{H} \quad : 5,33 \text{ (s)}$$

H <sub>6</sub> :	5,18
H <sub>7</sub> :	5,79 (m)
25 N-NH-CH :	9,56 (d), 9,64 (d)
-CH=CH-CH <sub>2</sub> :	7,07 (d, J=15,5) delta E
-CH=CH-CH <sub>2</sub> :	6,36 (m)
H du thiéno[3,2-c]pyridine :	8 à 9,71
aromatiques et H <sub>5</sub> thiazole :	6,70 à 6,78 ; 6,85 (s,1)
30 H mobiles :	12,56

**EXEMPLE 12** : [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinolénium trifluoroacétate iodhydrate.

35 **STADE A** : [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinolénium iodure.

40 On opère comme au stade B de l'exemple 6 au départ de 2,48 g de dérivé iodé préparé comme au stade B de l'exemple 11 et 1,04 cm<sup>3</sup> d'isoquinoléine. On obtient 1,26 g de produit attendu.

45 **STADE B** : [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinolénium trifluoroacétate iodhydrate.

On opère comme au stade C de l'exemple 6 en utilisant 1,26 g du produit obtenu au stade A et obtient 0,673 g de produit attendu.

50 RMN (DMSO 300 MHz)

55 
$$\text{=N-O-}\underline{\text{CH}}\text{-CO}_2\text{H} \quad : 5,32 \text{ (s)}$$

H <sub>6</sub> :	5,17 (m)
H <sub>7</sub> :	5,77 (m)

S-CH <sub>2</sub> :	3,07
N-NH-CH :	9,54 (d), 9,62 (d)
-CH=CH-CH <sub>2</sub> :	7,10 delta E
-CH=CH-CH <sub>2</sub> :	6,37 (m) delta E
5 -CH=CH-CH <sub>2</sub> - :	5,53 (d)
H de l'isoquinoléine :	8,9 à 10,06
aromatiques et H <sub>5</sub> thiazole :	6,45 à 6,37 (3H) ; 6,85 (s) 1H
H mobiles :	7,30 (2H) ; 9 (2H)

10 **EXEMPLE 13 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] 2-propényl] 2-méthyl 1H-imidazo[4,5-c] pyridinium trifluoroacétate iodhydrate.

15 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-(3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 2-méthyl 1H-imidazo[4,5-c]pyridinium iodure.

On opère comme au stade B de l'exemple 6 au départ de 1,92 g de dérivé iodé préparé comme au stade B de l'exemple 11 et 0,29 g de 2-méthyl 1H-imidazo[4,5-c]pyridine. On obtient 1,055 g de produit attendu.

20 **STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 2-méthyl 1H-imidazo[4,5-c] pyridinium trifluoroacétate iodhydrate.

25 On opère comme au stade C de l'exemple 6 en utilisant 1,043 g du produit obtenu au stade A et obtient 0,608 g de produit attendu.

RMN (DMSO 300 MHz)



35 H <sub>6</sub> :	5,15 (d, dédoublé)
H <sub>7</sub> :	5,77 (m, d, dédoublé après échange)
S-CH <sub>2</sub> :	3,76 (d), 3,61 (masqué)
N-NH-CH :	9,55 (d), 9,63 (d)
-CH=CH-CH <sub>2</sub> :	6,95 (dl)
40 -CH=CH-CH <sub>2</sub> :	6,35 (dt) delta E
-CH=CH-CH <sub>2</sub> - :	5,42 (m)
CH <sub>3</sub> de l'imidazopyridine :	2,70 (s)
H de la pyridine :	8,16 à 9,47
aromatiques et H <sub>5</sub> thiazole :	6,65 à 6,80 (m) 3H ; 6,86 (s) 1H
45 H mobiles :	7,34 (2H) ; 9,05 (m)

50 **EXEMPLE 14 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N,N-triméthyl 2-propén-1-aminium trifluoroacétate iodure

**STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 3-[7-[[[1-(3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N,N-triméthyl 2-propén-1-aminium iodure.

55 On agite pendant 40 minutes à température ambiante, 365 mg de dérivé iodé comme au stade B de l'exemple 11, 0,7 cm<sup>3</sup> de tétrahydrofurane et 220 microlitres d'une solution de triméthylamine dans l'éther (2,37 M/l). On ajoute 20 cm<sup>3</sup> d'éther, sépare le précipité, le chromatographie sur silice (éluant : chlorure de méthylène-méthanol 92-8), reprend le résidu à l'éther et obtient après élimination du solvant 276 mg de produit attendu.

Infra Rouge

 $=C-NH$  3404  $cm^{-1}$  + associé

5

	1791 $cm^{-1}$ (bêta lactame)
$\geq O$	1728 $cm^{-1}$ esters
	1685 $cm^{-1}$ amide

10

15

	1632 $cm^{-1}$ (épaulement)
	1613 $cm^{-1}$
Systeme conjugué	1596 $cm^{-1}$
+ amide II	1586 $cm^{-1}$
+ aromatique	1525 $cm^{-1}$
	1517 $cm^{-1}$
	1496 $cm^{-1}$

20

25

Ultra Violet

1) Dans l'éthanol + 1cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub>

30

infl. 219 nm	epsilon = 74000
max. 281 nm	epsilon = 23600
infl. 295 nm	epsilon = 22100

infl. 265, 276 nm

35

2) Dans l'éthanol HCl 0,1n

infl. 219 nm	epsilon = 75000
max. 283 nm	epsilon = 30000

40

**STADE B** : [6R-[3(E), 6alpha, 7bêta(Z)] 3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N,N-triméthyl 2-propén-1- aminium trifluoroacétate iodure.

45

On agite 1 heure à température ambiante 247 mg de produit obtenu au stade A avec 2,5 cm<sup>3</sup> d'acide trifluoroacétique à 10% d'anisole. On ajoute 25 cm<sup>3</sup> d'éther isopropylique, agite 10 minutes, isole le précipité formé et sèche sous pression réduite à 20°C pendant 24 heures. On obtient 128 mg de produit attendu.

RMN (DMSO 300 MHz)

50



55

H <sub>6</sub> :	5,16 (d)
H <sub>7</sub> :	5,76 (d)
N-NH-CH :	9,08 (d)
-CH=CH-CH <sub>2</sub> :	6,07 (m) delta E

-CH=CH-CH<sub>2</sub> : 7,04 (d)  
 -CH=CH-CH<sub>2</sub>- : 4,05 (d)  
<sup>⊕</sup>N-(CH<sub>3</sub>)<sub>3</sub> : 2,99 (s), 3,03 (s)  
 aromatiques et H<sub>5</sub> thiazole : 6,70 à 6,9

5

**EXEMPLE 15 :** [6R-[3(E), 6alpha, 7bêta(Z)]] [3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N-(cyanométhyl) N,N-diméthyl 2-propén-1-aminium] trifluoroacétate iodure.

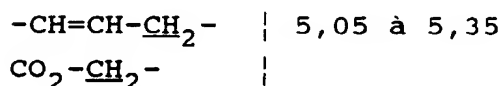
10 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] [3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N-(cyanométhyl) N,N-diméthyl 2-propén-1-aminium] iodure.

15 On opère comme au stade A de l'exemple 14 à partir de 250 mg de dérivé iodé et 250 cm<sup>3</sup> d'une solution de diméthylamino acétonitrile dans le tétrahydrofurane (1-9). On obtient 172 mg de produit attendu.

RMN (CDCl<sub>3</sub> 400 MHz)

-CH=CH-CH<sub>2</sub> : 6,05 (d,t) delta E

20



25

<sup>⊕</sup>N-CH<sub>2</sub>-CN : 4,35 à 4,5  
 les CH<sub>3</sub> : 3,07 à 3,9

30 **STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] [3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N-(cyanométhyl) N,N-diméthyl 2-propén-1-aminium] trifluoroacétate iodure.

35 On opère comme au stade B de l'exemple 14 à partir de 172 mg de produit préparé au stade A. On obtient 72 mg de produit attendu.

RMN (DMSO 300 MHz)

40



45 H<sub>6</sub> : 5,20 (d)  
 H<sub>7</sub> : 5,82 (m)  
 N-NH-CH : 9,54 (d)  
 -CH=CH-CH<sub>2</sub> : 7,1 (d)  
 -CH=CH-CH<sub>2</sub>- : 6,13 (m)  
 -CH=CH-CH<sub>2</sub>- : 4,24 (d)  
 50 <sup>⊕</sup>N-(CH<sub>3</sub>)<sub>2</sub> : 3,19 (s)  
<sup>⊕</sup>N-CH<sub>2</sub>-CN : 4,8 (s)  
 aromatiques et H<sub>5</sub> thiazole : 6,65 à 6,80 et 6,87  
 H mobiles : 7,79 ; 9,07

55



**EXEMPLE 16 :** [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) [3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propén-1-aminium] trifluoroacétate iodure.

5 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) [3-[7-[[1-(3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl) 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propén-1-aminium] iodure.

10 On mélange 1 heure à 20°C 350 mg de dérivé iodé obtenu comme indiqué au stade B de l'exemple 11 avec 1,6 cm<sup>3</sup> d'acétonitrile et 27 mg de diméthylaminoacétamide. On élimine les solvants sous pression réduite, chromatographie le résidu sur silice (éluant : chlorure de méthylène-méthanol 97-3 puis 92-8). On recueille 300 mg de produit attendu.

15 RMN (CDCl<sub>3</sub> 300 MHz)

-CH=CH-CH<sub>2</sub>- : 6,10 delta E

-CH=CH-CH<sub>2</sub>- : 4,56

20 
$$\begin{array}{c} \text{--CH=CH-CH}_2 \\ \text{H aromatiques} \\ \text{NH}_2 \end{array} \quad 6,85 \text{ à } 7,37$$

25 les CH<sub>3</sub> : 3,24 à 3,35  
<sup>+</sup>N-CH<sub>2</sub>-C : 4,23 (m)

30 **STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) [3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo-[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propén-1-aminium] trifluoroacétate iodure.

On opère comme au stade B de l'exemple 14 à partir de 285 mg de produit préparé au stade A ci-dessus. On obtient 152 mg de produit attendu.

35 RMN (DMSO 300 MHz)

40 
$$\text{=N-O-CH-CO}_2\text{H} \quad : 5,34 \text{ (s)}$$

45 H<sub>6</sub> : 5,19 (d)  
 H<sub>7</sub> : 5,85 (m)  
 les NH : 9,55 (d) ; 9,62 (d)  
 -CH=CH-CH<sub>2</sub>- : 7,03 (d, J=13,5) delta E)  
 -CH=CH-CH<sub>2</sub>- : 6,13 (m)  
 -CH=CH-CH<sub>2</sub>- : 4,27 (d)  
<sup>+</sup>N-(CH<sub>3</sub>)<sub>2</sub> : 3,19 (s)  
 50 <sup>+</sup>N-CH<sub>2</sub>- : 4,01 (s)  
 aromatiques et H<sub>5</sub> thiazole : 6,72 à 6,8

H mobiles

55

**EXEMPLE 17 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium trifluoroacétate iodure.

5 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] [3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium iodure.

10 On dissout à 20°C, 357 mg de dérivé iodé obtenu comme indiqué au stade B de l'exemple 11 dans 7 cm<sup>3</sup> d'éther et 1,3 cm<sup>3</sup> de chlorure de méthylène. On ajoute 130 microlitres de méthylpyrrolidine, ajoute 5 cm<sup>3</sup> d'éther, agite 10 minutes, isole le précipité et le sèche à 20°C sous pression réduite. On obtient 300 mg de produit attendu.

15 **STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium trifluoroacétate iodure.

On opère comme au stade B de l'exemple 14 à partir de 290 mg de produit obtenu au stade A ci-dessus. On obtient 150 mg de produit attendu.

20 RMN (DMSO 300 MHz)



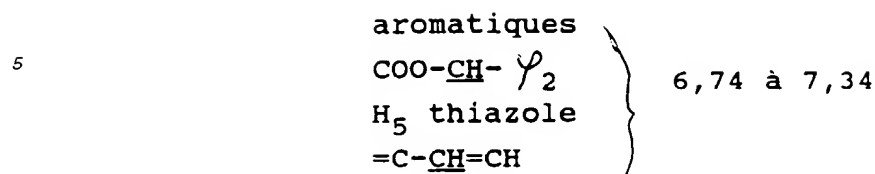
H <sub>6</sub> :	5,18 (d)
H <sub>7</sub> :	5,79 (m)
les -NH-CH :	9,52 (d) ; 9,61 (d)
30 -CH=CH-CH <sub>2</sub> :	7,05 (d, J=15) delta E
-CH=CH-CH <sub>2</sub> :	6,17 (m) delta E
-CH=CH-CH <sub>2</sub> - :	4,11 (d)
<sup>+</sup> N-CH <sub>3</sub> :	2,99 (s)
pyrrolidine :	2,10 (sl), 3,45 (sl)
35 aromatiques et H <sub>5</sub> thiazole :	6,65 à 6,85
H mobiles :	9,10

**EXEMPLE 18 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[[(2-amino 4-thiazolyl) [(R) 1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno [2,3-b] pyridinium trifluoroacétate iodhydrate.

40 **STADE A :** [6R-[3(E), 6alpha, 7bêta (Z)]] p-méthoxybenzyl 7-[[[(R) 1-(3,4-dihydroxy) phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl 2-carboxylate.

45 On agite pendant 5 minutes 1,1 g d'acide [[(R) (3,4-dihydroxyphényl) (diphénylméthoxycarbonyl) méthoxy] imino] [2-(triphénylméthylamino) 4-thiazolyl] acétique isomère syn (préparé comme indiqué pour l'isomère S dans les Brevets européens EP 2 266 060 et 0 280 521 ou dans le brevet allemand DE 37 42 457 A1) dans 11,36 cm<sup>3</sup> de chlorure de méthylène. On refroidit à -5°C la solution obtenue, ajoute 403,4 mg de dicyclocarbondiimide, agite 40 minutes et ajoute 50 668 mg de chlorhydrate de p-méthoxybenzyle 7-amino 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-2-carboxylate préparé comme indiqué dans le brevet européen EP 0 333 154. On agite 3 heures en laissant revenir à température ambiante, élimine les solvants, chromatographie le résidu sur silice (éluant : chlorure de méthylène-acétate d'éthyle 9-1) et obtient 712 mg de produit attendu.

55

RMN (CDCl<sub>3</sub> 300 MHz)

10

$-\underline{\text{CH}}=\text{CH}-\text{CH}_2$  : 6,25 (d, J=1) delta Z

15

$-\text{CH}=\text{CH}-\underline{\text{CH}}_2$		3,73 (dd)
		3,92 (dd)

20

$\text{CO}_2-\underline{\text{CH}}_2-$		5,18 (s)
		5,24

$\varphi-\underline{\text{OCH}}_3$  : 3,81 (s)

25

STADE B : [6R-[3(E), 6alpha, 7bêta (Z)]] p-méthoxybenzyl 7-[[[(R)-1-[3,4-[(dihydroxy) phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-iodo 1-propényl) 8-oxo 5-thia 1-azabicyclo [4,2,0]oct-2-èn-3-yl 2-carboxylate.

30

On agite pendant 2 heures à température ambiante un mélange de 590 mg de produit obtenu au stade A, 11,9 cm<sup>3</sup> d'acétone et 216 mg d'iodure de sodium, évapore le solvant puis reprend le résidu par 5 cm<sup>3</sup> de chlorure de méthylène. On lave la solution par 3 fois 10 cm<sup>3</sup> de thiosulfate de sodium puis par 2 fois 10 cm<sup>3</sup> d'une solution aqueuse de chlorure de sodium. On sèche, cristallise dans l'éther, et obtient 456,6 mg de produit attendu.

35

RMN (CDCl<sub>3</sub> 400 MHz)



45

$\text{H}_6$ : $\text{H}_7$ : $\text{S}-\underline{\text{CH}}_2$ : $\text{C}-\underline{\text{NH}}-\text{CH}$ : $-\text{CH}=\underline{\text{CH}}-\text{CH}_2$ : $-\text{CH}=\text{CH}-\underline{\text{CH}}_2-$ : $-\text{CO}_2-\underline{\text{CH}}_2-\varphi$ : $\varphi-\text{O}-\text{CH}_3$ : aromatiques et H <sub>5</sub> thiazole :	4,85 (d) 5,74 (dd) 3,24 8,10 (d) 6,00 (d, J=15,5 et 17,5) delta E 3,82 (d), 3,98 (d) 5,24 3,80 (s) 6,68 à 7,40
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50

STADE C : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[[(R)-1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(p-méthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno-[2,3-b]pyridinium iodure.

55

On agite et triture pendant deux heures à température ambiante 446 mg de dérivé iodé obtenu au stade B et 0,44 cm<sup>3</sup> de thiéno pyridine. On ajoute de l'éther et sèche sous pression réduite pendant 24 heures le solide obtenu. On obtient 442 mg de produit attendu.

RMN

=N-O-CH-φ : 5,55  
 -CH=CH-CH<sub>2</sub> : 6,30 (m) delta E

5



10

H du thiéno pyridine : 7,89 à 9,21

**STADE D** : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [(R) 1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno [2,3-b] pyridinium trifluoroacétate iodhydrate.

15

On agite 1 heure à température ambiante 632 mg de produit obtenu comme au stade C dans 6,32 cm<sup>3</sup> d'une solution d'acide trifluoroacétique à 10% d'anisole. On refroidit à +5°C, ajoute 65 cm<sup>3</sup> d'éther isopropylique, agite 10 minutes, filtre et sèche sous pression réduite à température ambiante pendant 16 heures. On obtient 403 mg de produit attendu.

20

RMN (DMSO 400 MHz)

25



H<sub>6</sub> : 5,18 (d)  
 H<sub>7</sub> : 5,77 (dd)  
 S-CH<sub>2</sub> : 3,73 (m)  
 -CH-CH-CH<sub>2</sub> : 7,15 (d, J=16) delta E  
 -CH=CH-CH<sub>2</sub> : 6,30 (d,t)

35

-CH=CH-CH<sub>2</sub>- : 5,68 (d)  
 H du thiéno pyridine : 7,88 à 9,23  
 aromatiques, NH, H<sub>5</sub> thiazole : 6,70 à 7,35 (≈ 6H)  
 H mobiles : 7,31 à 9,61

40

**EXEMPLE 19** : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [(S)-1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b] pyridinium trifluoroacétate iodure.

**STADE A** : [6R-[3(E), 6alpha, 7bêta(Z)]] p-méthoxybenzyl 7-[[[(S) 1-[3,4-dihydroxy phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-èn-3-yl] 2-carboxylate.

45

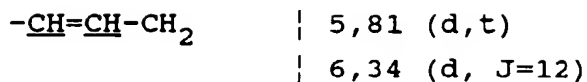
On opère comme au stade A de l'exemple 18 en utilisant au départ 678 mg d'acide [(S) (3,4-dihydroxyphényl) (diphénylméthoxycarbonyl) méthoxy] imino] [2-(triphénylméthylamino) 4-thiazolyl] acétique isomère syn préparé comme indiqué dans les brevets européens EP 0 266 060 et 0 280 521 ou dans le brevet allemand DE 37 32 457 A1 et 412 mg de chlorhydrate de p-méthoxybenzyl de 7-amino 3-(3-chloro 1-propényl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-èn 2-carboxylate. On obtient 590 mg de produit attendu.

50

RMN (CDCl<sub>3</sub> 400 MHz)

55

=N-O-CH- : 5,89 (s)



5 STADE B : [6R-[3(E), 6alpha, 7bêta(Z)]] p-méthoxybenzyl 7-[[[(S)-1-[3,4-[(dihydroxy) phényl] 2-(diphénylméthoxy) 2-oxoéthoxy] imino] [2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 3-(3-iodo 1-propényl) 8-oxo 5-thia 1-azabi-cyclo [4,2,0]oct-2-èn-3-yl 2-carboxylate.

10 On opère comme au stade B de l'exemple 18 en utilisant 850 mg du produit obtenu au stade A et 335 mg d'iodure de sodium. On obtient 595 mg de produit attendu.

Infra Rouge (CHCl<sub>3</sub>)

15		3548 cm <sup>-1</sup>	
	OH	3478 cm <sup>-1</sup>	
	NH	3401 cm <sup>-1</sup>	
20		3284 cm <sup>-1</sup>	
		1772 cm <sup>-1</sup>	bêta lactame
25	>C=O	1725 cm <sup>-1</sup>	ester
		1684 cm <sup>-1</sup>	amide
		1614 cm <sup>-1</sup>	
30	aromatique	1601 cm <sup>-1</sup>	
	hétérocycle	1586 cm <sup>-1</sup>	
	amide II	1529 cm <sup>-1</sup>	
35	>C=C<	1517 cm <sup>-1</sup>	
		1496 cm <sup>-1</sup>	

40 Ultra Violet

1) dans le dioxane :

	infl. 224 nm	E <sub>1</sub> <sup>1</sup> = 566	epsilon = 69600
45	infl. 242 nm	E <sub>1</sub> <sup>1</sup> = 345	
	infl. 275 nm	E <sub>1</sub> <sup>1</sup> = 197	
	max. 282 nm	E <sub>1</sub> <sup>1</sup> = 201	epsilon = 24700
	infl. 290 nm	E <sub>1</sub> <sup>1</sup> = 195	
50	max. 314 nm	E <sub>1</sub> <sup>1</sup> = 218	epsilon = 26800

2) dans le dioxane/HCl 0,1N

	max. 285 nm	E <sub>1</sub> <sup>1</sup> = 266	epsilon = 32700
55	infl. 304 nm	E <sub>1</sub> <sup>1</sup> = 244	epsilon = 30000
	infl. 320 nm	E <sub>1</sub> <sup>1</sup> = 188	epsilon = 23100

STADE C : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[[(S)-1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(p-méthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b] - pyridinium iodure.

5 On opère comme au stade C de l'exemple 18 en utilisant 430 mg de dérivé iodé obten au stade B et 470 mg de thiéno pyridine. On obtient 438 mg de produit attendu.

Infra Rouge ( $\text{CHCl}_3$ )

10 Région NH/OH complexe

		1780 $\text{cm}^{-1}$ bêta lactame
15	-C=O	1725 $\text{cm}^{-1}$ ester
		1684 $\text{cm}^{-1}$ amide
		1613 $\text{cm}^{-1}$
20		1600 $\text{cm}^{-1}$
	aromatique	1586 $\text{cm}^{-1}$
	hétérocycle	1575 $\text{cm}^{-1}$
25	Amide II	1558 $\text{cm}^{-1}$
	+ >C=C<	1525 $\text{cm}^{-1}$
		1516 $\text{cm}^{-1}$
30		1496 $\text{cm}^{-1}$

STADE D : [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [[(S)-1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b] pyridinium trifluoroacétate iodure.

35 On opère comme au stade D de l'exemple 18 en utilisant 400 mg de produit obtenu au stade C. On obtient 275 mg de produit attendu.

40 RMN (DMSO 400 MHz)



45

$\text{H}_6$ :	5,15
$\text{H}_7$ :	5,80 (dd, sl après échange)
CO-NH- :	9,55 (d)
C-NH-CH :	9,55 (d)
50 S-CH <sub>2</sub> :	3,51 (m)
-CH-CH-CH <sub>2</sub> :	7,13 (d, J=16) delta E
-CH=CH-CH <sub>2</sub> :	6,27 (d,t J=16 et 6)
-CH=CH-CH <sub>2</sub> - :	5,67 (d, J=6)
H du thiéno pyridine :	7,89 à 9,55
55 aromatiques et H <sub>5</sub> thiazole :	6,60 à 6,87 (m)

**EXEMPLE 20 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1,2-diméthylimidazo [4,5-c]pyridinium trifluoroacétate iodhydrate.

5 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-(3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1,2-diméthylimidazo[4,5-c]pyridinium iodure.

10 On agite pendant 1 heure 1,08 g de produit obtenu comme indiqué au stade B de l'exemple 11 avec 170 mg de 1,2-diméthyl 4-aza benzimidazole dans 0,9 cm<sup>3</sup> d'acétonitrile. On ajoute 40 cm<sup>3</sup> d'éther, filtre le précipité, le rince à l'éther et le sèche 16 heures sous pression réduite. Après chromatographie sur silice (éluant : chlorure de méthylène-méthanol 94-6), on obtient 306 mg de produit attendu.

15 **STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0] oct-2-en-3-yl] 2-propényl] 1,2-diméthylimidazo [4,5-c] pyridinium trifluoroacétate iodhydrate.

On opère comme à l'exemple 14 stade B à partir de 297 mg de produit obtenu au stade A. On obtient 155 mg de produit attendu.

20 RMN (DMSO 400 MHz)

25 
$$\begin{array}{l} \text{=N-O-}\underline{\text{CH}}\text{-CO}_2\text{H} \\ \text{et CH=CH-}\underline{\text{CH}}_2 \end{array} \quad \begin{array}{l} : 5,40 \text{ (s1)} \\ : 5,30 \text{ (s)} \quad 3\text{H} \end{array}$$

30  $\begin{array}{ll} \text{H}_6 : & 5,13 \text{ (d)} \\ \text{H}_7 : & 5,75 \text{ (m)} \\ \text{C-NH-CH} : & 9,63 \text{ (d), } 9,65 \text{ (d)} \\ \text{-}\underline{\text{CH}}\text{-CH-CH}_2 : & 6,98 \text{ (d, J=15,5) delta E} \\ \text{-CH=}\underline{\text{CH}}\text{-CH}_2 : & 6,30 \text{ (d,t)} \\ \text{les CH}_3 : & 2,71 \text{ (s), } 3,92 \text{ (s)} \end{array}$

35  $\begin{array}{ll} \text{imidazopyridine} : & 8,28 \text{ à } 9,48 \\ \text{aromatiques et H}_5 \text{ thiazole} : & 6,66 \text{ à } 6,85 \\ \text{H mobiles} : & 9,00, 9,08 \end{array}$

40 **EXEMPLE 21 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 2,3-diméthylimidazo[4,5-c] pyridinium trifluoroacétate iodhydrate.

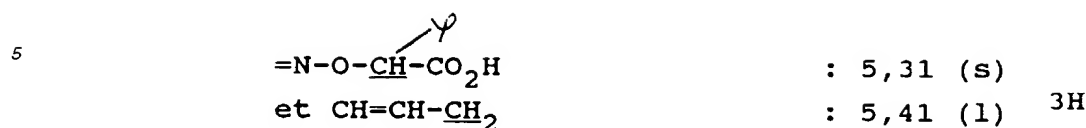
45 **STADE A :** [6R-[3(E), 6alpha, 7bêta (Z)]] 5-[3-[7-[[[1-(3,4bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 2,3-diméthylimidazo[4,5-c]pyridinium iodure.

On opère comme indiqué au stade A de l'exemple 20 en utilisant 1,92 g de produit obtenu comme au stade B de l'exemple 11 et 303 mg de 2,3-diméthyl 4-aza benzimidazole. On obtient 877 mg de produit attendu.

50 **STADE B :** [6R-[3(E), 6alpha, 7bêta (Z)]] 5-[3-[7-[[[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 2,3-diméthylimidazo [4,5-c] pyridinium trifluoroacétate iodhydrate.

55 On opère comme au stade B de l'exemple 14 à partir de 865 mg de produit obtenu au stade A. On obtient 488 mg de produit attendu.

RMN (DMSO 400 MHz)



10 H<sub>6</sub> : 5,15 (d, dédoublé)  
 H<sub>7</sub> : 5,76  
 C-NH-CH : 9,53 (d), 9,60 (d)



20 les CH<sub>3</sub> : 2,75 (s), 3,94 (s)  
 imidazopyridine : 8,18 à 9,58  
 aromatiques et H<sub>5</sub> thiazole : 6,65 à 6,86  
 H mobiles : 7,31 à 9,60

25 **EXEMPLE 22 :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] quino-  
 léinium trifluoroacétate iodhydrate.

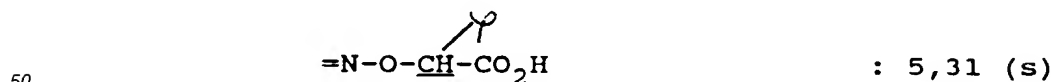
30 **STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[1-(3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] quinoléinium iodure.

35 On opère comme au stade B de l'exemple 6 au départ de 2,50 g de dérivé iodé préparé comme au stade B de l'exemple 11 et 0,63 g de quinoléine. On obtient 2,40 g de produit attendu que l'on purifie par chromatographie sur silice (éluant : chlorure de méthylène-méthanol 95-5).

40 **STADE B :** [6R-[3(E), 6alpha, 7bêta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] quinoléinium trifluoroacétate iodhydrate.

On opère comme au stade B de l'exemple 14 en utilisant 1,65 g du produit obtenu au stade A et obtient 0,94 g de produit attendu.

45 RMN (DMSO 400 MHz)



55 H<sub>6</sub> : 5,14 (d)  
 H<sub>7</sub> : 5,75 (m)  
 C-NH-CH : 9,48 (d), 9,52 (d)  
 -CH-CH-CH<sub>2</sub> : 6,97 (d, J=15) delta E  
 -CH=CH-CH<sub>2</sub> : 5,89 (m)  
 H de la quinoléine : 8,07 à 9,59  
 aromatiques et H<sub>5</sub> thiazole : 6,64 à 6,77 ; 6,85 (s)



H mobiles :

9,03 à 9,52

**EXEMPLE 23 :** [6R-[3(E),6alpha,7bêta(Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 4-éthylthio pyridinium trifluoroacétate iodhydrate.

**STADE A :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[1-[3,4-bis[(2-méthoxy éthoxy) méthoxy] phényl] 2-[(diphénylméthoxy) 2-oxoéthoxy] imino] 2-[(triphénylméthyl) amino] 4-thiazolyl] acétyl] amino] 2-[(paraméthoxybenzyloxy) carbonyl] 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 4-éthylthio pyridinium iodure.

On opère comme au stade B de l'exemple 6 au départ de 2,50 g de dérivé iodé préparé comme au stade B de l'exemple 11 et 1 cm<sup>3</sup> de 4-éthylthio pyridine. On obtient 2,45 g de produit attendu que l'on purifie par chromatographie sur silice (éluant : chlorure de méthylène-méthanol 95-5).

**STADE B :** [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxy phényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 4-éthylthio pyridinium trifluoroacétate iodhydrate.

On opère comme au stade B de l'exemple 14 en utilisant 1,54 g du produit obtenu au stade A et obtient 0,807 g de produit attendu.

RMN (DMSO 400 MHz)



H<sub>6</sub> : 5,16  
 H<sub>7</sub> : 5,77 (m)  
 C-NH-CH : 9,47 (d)



H de la pyridine : 7,97 à 8,69  
 aromatiques et H<sub>5</sub> thiazole : 6,67 à 6,78 ; 6,87 (s)  
 H mobiles : 9,04 à 13,80

**EXEMPLE 24 :** On a réalisé des préparations pour injections de formule :

- Produit de l'exemple 2 500 mg
- Excipient aqueux stérile q.s.p. 5 cm<sup>3</sup>

#### ETUDE PHARMACOLOGIQUE DES PRODUITS DE L'INVENTION

Activité in vitro, méthode des dilutions en milieu solide.

On prépare une série de boîtes dans lesquelles on répartit une même quantité de milieu nutritif stérile, contenant des quantités croissantes du produit à étudier puis chaque boîte estensemencée avec plusieurs souches bactériennes.

Après incubation de 24 heures en étuve à 37°C, l'inhibition de la croissance est appréciée par l'absence de tout développement bactérien ce qui permet de déterminer les concentrations minimales inhibitrices (CMI) exprimées en microgrammes/cm<sup>3</sup>.

Les résultats sont exprimés en CMI<sub>90</sub> qui est la concentration minimum d'antibiotique permettant d'inhiber la croissance de 90 % des souches étudiées.

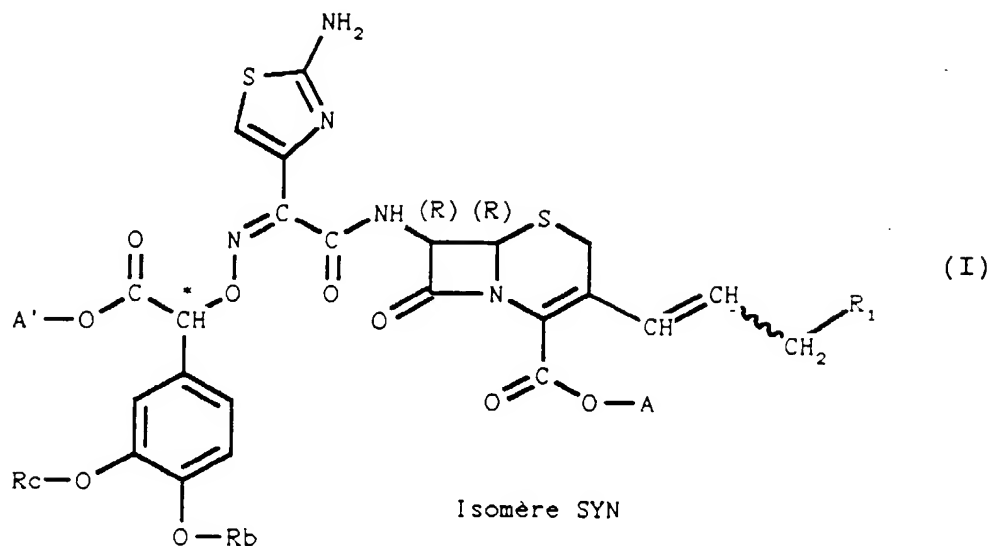
On a obtenu les résultats suivants :

Nombre de souches  Produit de l'exemple	Enterobacteries		Staphylocoques aureus oxacilline S 20	Proteus SPP  9	Pseudomonas Aeruginosa  40
	Cefotax.S 27	Cefotax.R 40			
2	0,3	5	0,6	0,15	1,25
4	0,3	5	1,25	0,3	5
9	0,6	10	1,2	0,6	2,5
12	0,3	10	0,6	0,3	10
16	0,6	10	1,2	0,6	2,5
17	0,6	10	1,2	0,6	1,2
18	0,15	2,5	0,3	0,3	2,5

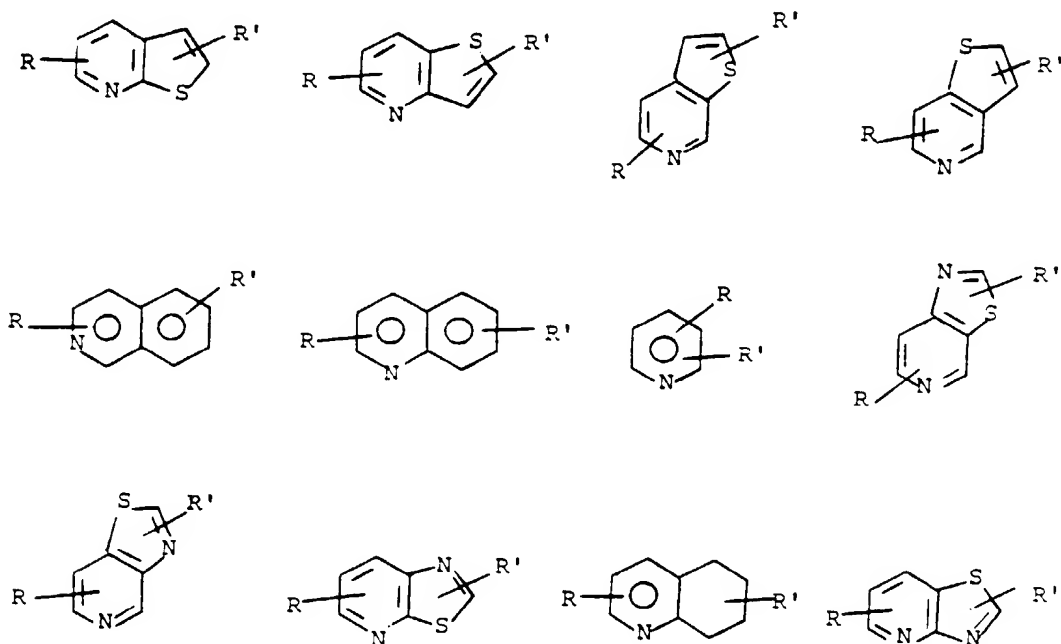
## Revendications

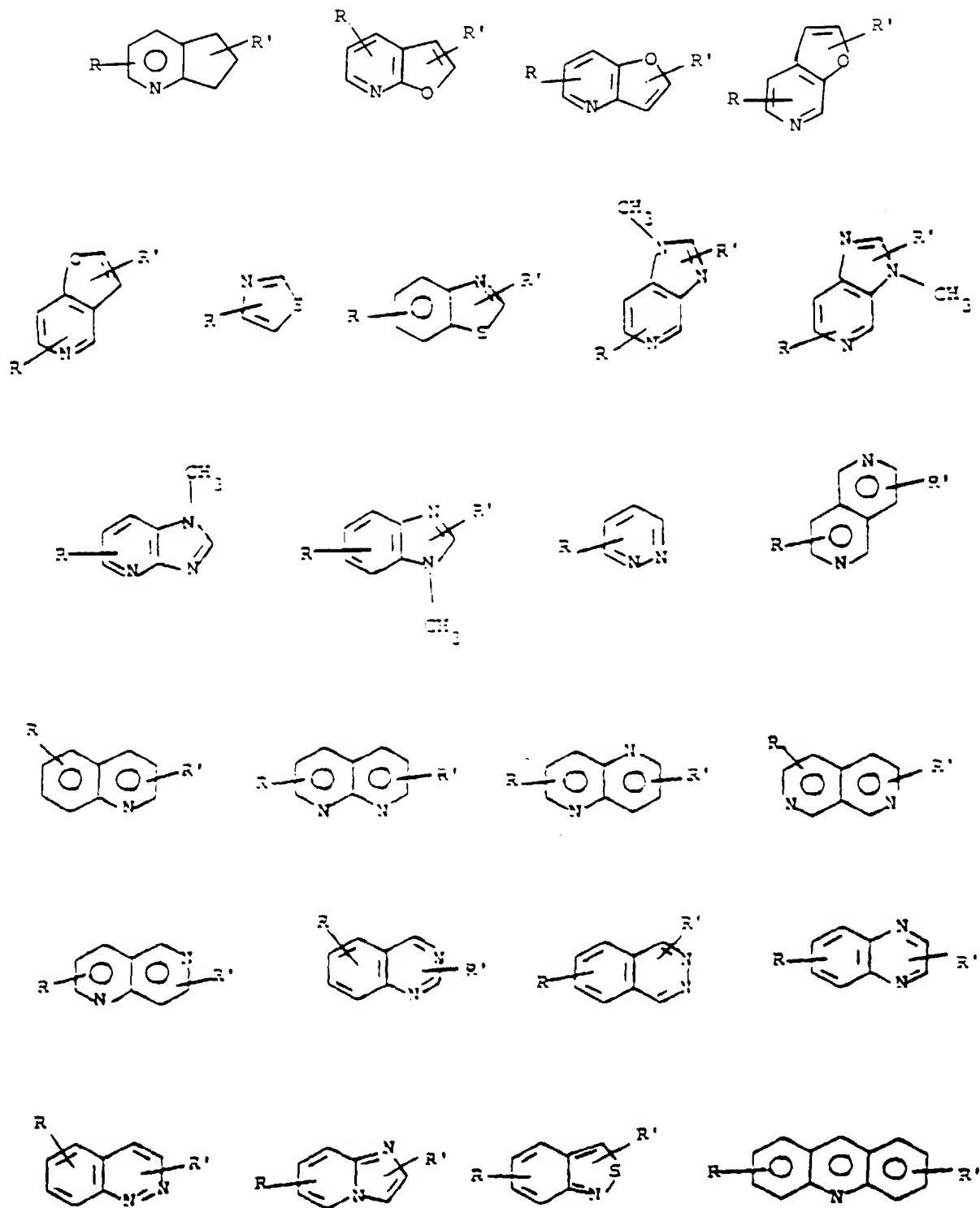
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

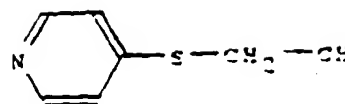
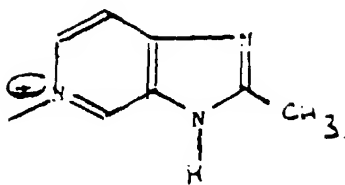
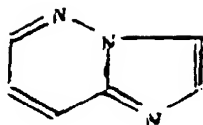
1. Les produits de formule générale (I) :



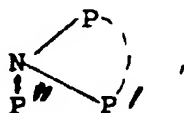
isomère syn, sous forme R ou S ou d'un mélange R, S, formule dans laquelle :  
 $R_1$  représente un radical choisi parmi les radicaux suivants :



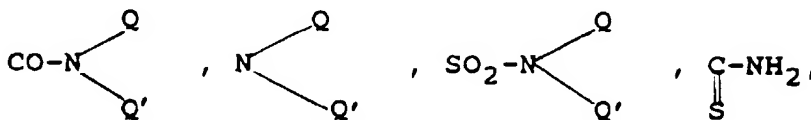




ou



sous forme d'ammonium quaternaire, l'expression sous forme d'ammonium quaternaire indiquant que le radical  $R_1$  est lié avec le groupement  $-\text{CH}=\text{CH}-\text{CH}_2-$  par le ou l'un des atomes d'azote qu'il comporte, dans lesquels R et R' identiques ou différents représentent un atome d'hydrogène, un radical alkyle renfermant de 1 à 4 atomes de carbone, un radical alcoxy renfermant de 1 à 4 atomes de carbone, un atome d'halogène, un radical  $\text{CO}_2-\text{Q}$ ,

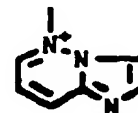
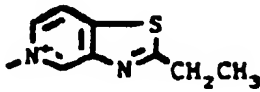
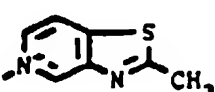
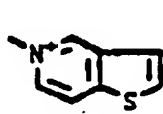
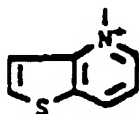
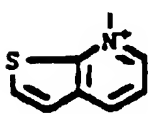


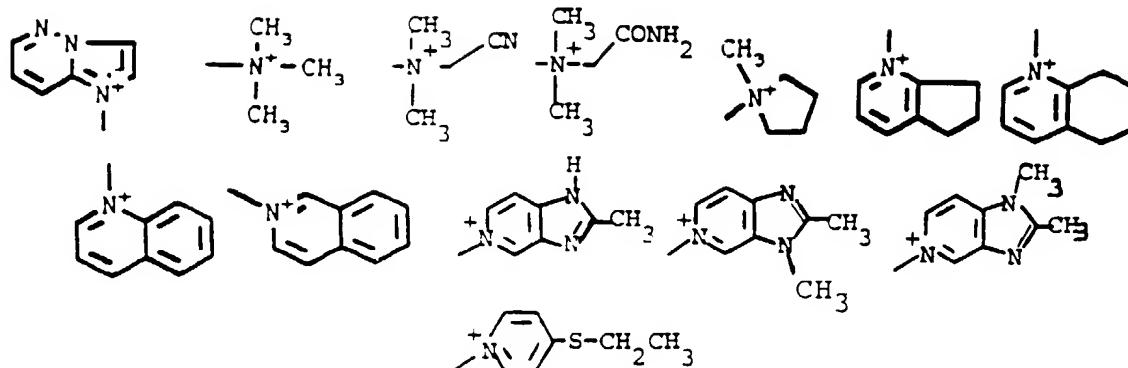
$\text{NH}-\text{CO}-\text{Q}$ ,  $\text{CN}-\text{CH}_2-\text{CN}$ ,  $\text{CH}_2-\text{SQ}$  dans lesquels Q et Q' identiques ou différents représentent un atome d'hydrogène ou un radical alkyle renfermant de 1 à 4 atomes de carbone, P, P' et P'' identiques ou différents représentent un radical alkyle renfermant au plus 4 atomes de carbone, éventuellement substitué par un des substituants indiqués ci-dessus pour R et R', le symbole } indiquant que P et P' peuvent éventuellement former avec l'atome d'azote auquel ils sont liés, un hétérocycle à 5 ou 6 chaînons.

$R_b$  et  $R_c$ , identiques ou différents représentent un atome d'hydrogène ou un groupement acyle, choisi parmi les radicaux acétyle, propionyle et benzoyle,

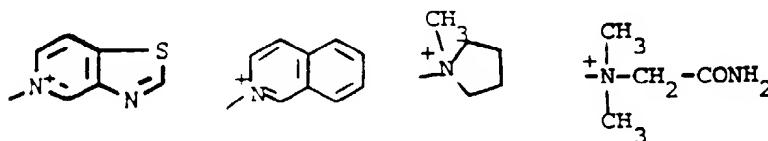
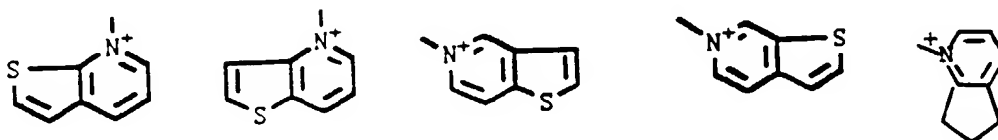
A et A' identiques ou différents représentent un atome d'hydrogène, un équivalent de métal alcalin, alcalino-terreux, de magnésium, d'ammonium ou d'une base organique aminée ou A et A' représentent le reste d'un groupement ester facilement clivable ou  $\text{CO}_2\text{A}$  représente  $\text{CO}_2^-$ ; le trait ondulé signifie que le groupement  $\text{CH}_2\text{R}_1$  peut se trouver dans la position E ou Z ainsi que les sels des produits de formule (I) avec les acides minéraux ou organiques.

2. Les produits de formule générale (I) telle que définie à la revendication 1 dans laquelle  $R_1$  est choisi parmi les radicaux suivants :

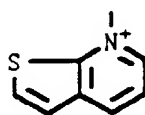




3. Les produits de formule générale (I) telle que définie à la revendication 1 ou 2 dans laquelle  $R_1$  est choisi parmi les radicaux :



4. Les produits de formule générale (I) telle que définie à la revendication 3 dans laquelle  $R_1$  représente le radical :



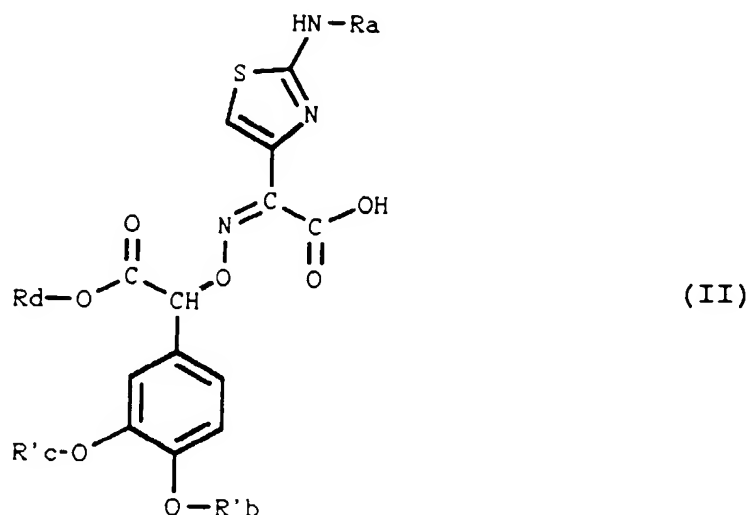
5. Le produit de formule générale (I) selon la revendication 1 dont le nom suit :

- le [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c] pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b] pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables et particulièrement sous forme S,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[[2-amino 4-thiazolyl] [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinoléinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins,

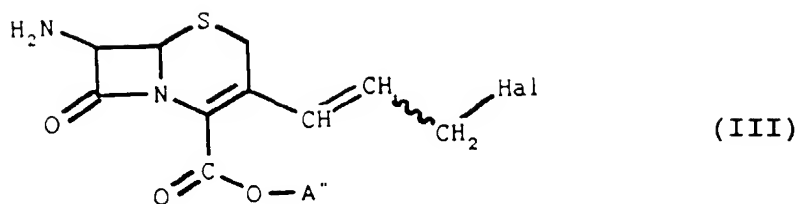
alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,

- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) 3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propén-1-aminium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables.

6. Procédé de préparation des produits de formule (I) telle que définie à la revendication 1, caractérisé en ce que l'on fait agir un produit de formule (II) :



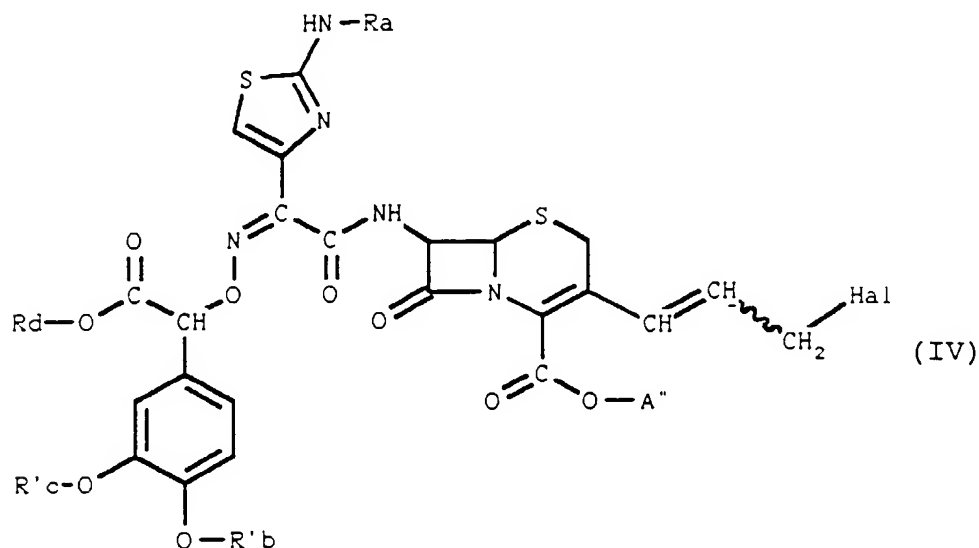
isomère syn, racémique ou optiquement actif ou un dérivé fonctionnel du produit de formule (II), dans laquelle  $R_a$  représente un atome d'hydrogène ou un groupement protecteur du radical amino,  $R'_b$  et  $R'_c$  identiques ou différents représentent un atome d'hydrogène ou un groupement protecteur du radical hydroxyle,  $R_d$  représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable, avec un produit de formule (III) :



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dans laquelle Hal représente un atome d'halogène, A'' représente un atome d'hydrogène ou le reste d'un groupe-  
ment ester facilement éliminable et le trait ondulé signifie que le groupement CH<sub>2</sub>Hal peut se trouver dans la  
position E ou Z pour obtenir un produit de formule (IV) :

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que l'on fait agir avec un réactif capable d'introduire le radical R<sub>1</sub> pour obtenir un produit de formule (V) :

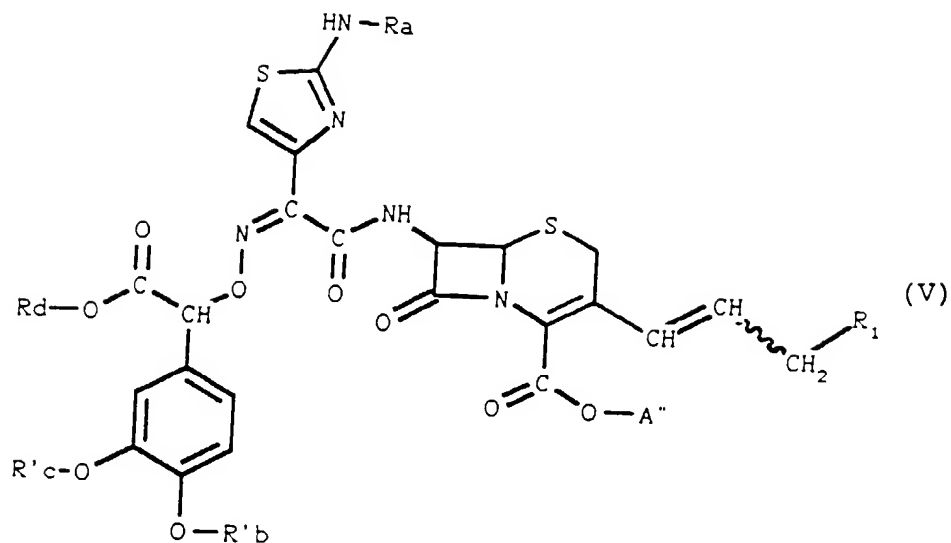
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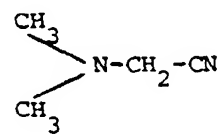
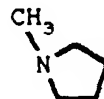
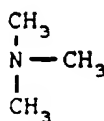
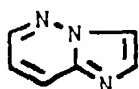
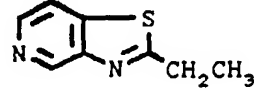
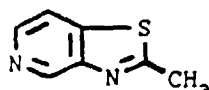
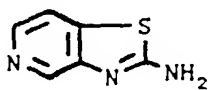
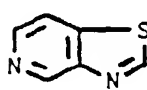
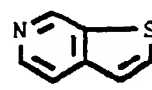
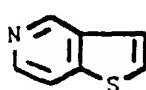
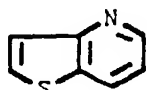
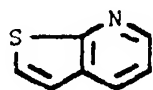


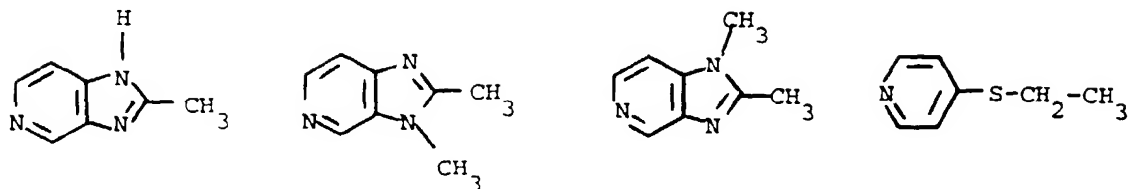
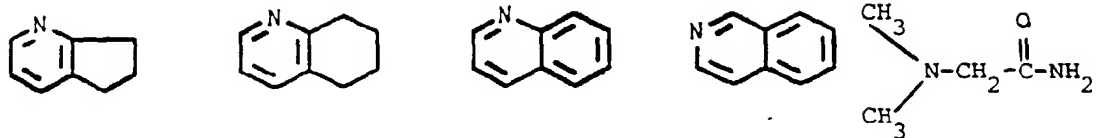


que, si désiré, l'on sépare en ses isomères E ou Z ou transforme les isomères Z en isomères E et produits de formule (V) que, si nécessaire ou si désiré, l'on soumet à une ou plusieurs des réactions suivantes, dans un ordre quelconque :

- a) coupure par hydrolyse ou par action de la thiourée de tout ou partie des groupements esters ou des groupements de protection du radical amino ou des radicaux hydroxyles,  
 b) estérification ou salification par une base du ou des radicaux carboxyliques,  
 c) salification par un acide du radical amino,  
 d) séparation des produits sous forme de mélange R,S en R ou S.

7. Procédé de préparation selon la revendication 6 caractérisé en ce que le réactif capable d'introduire le radical R<sub>1</sub> est choisi parmi les réactifs de formule :

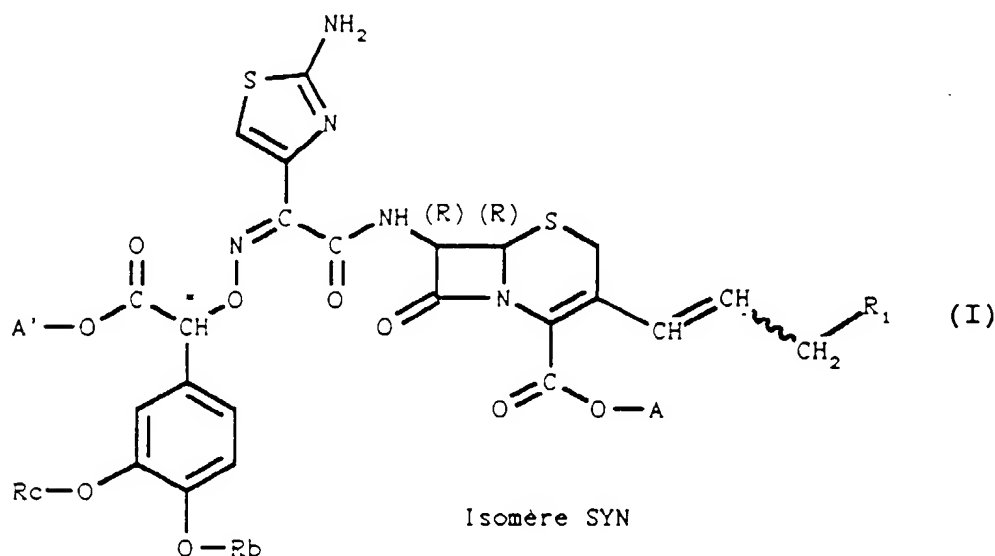




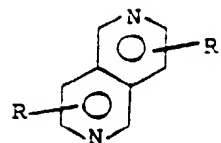
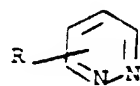
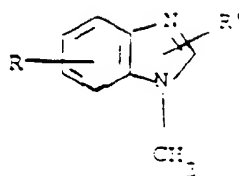
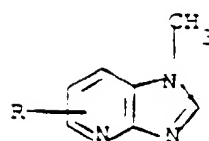
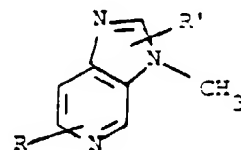
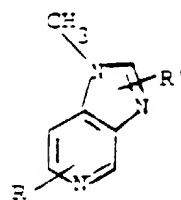
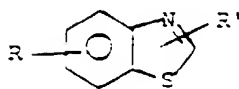
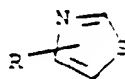
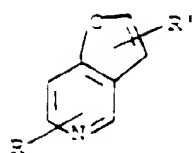
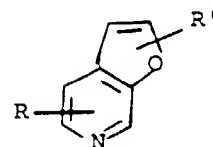
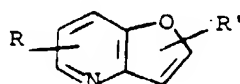
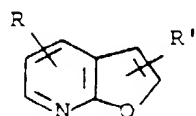
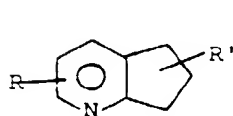
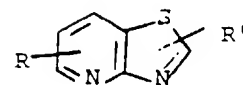
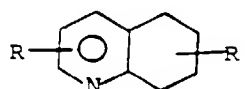
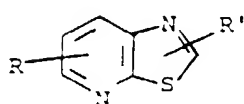
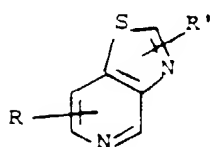
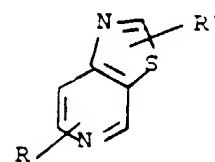
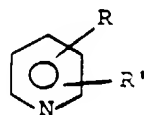
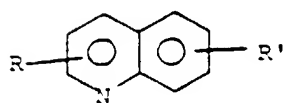
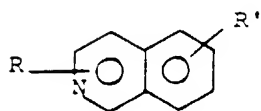
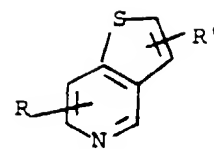
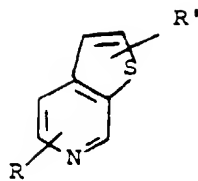
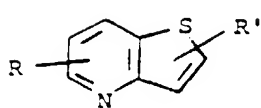
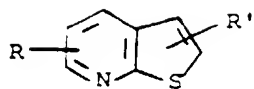
8. A titre de médicaments, les produits répondant à la formule (I) telle que définie à la revendication 1, ainsi que leurs sels d'acides, pharmaceutiquement acceptables.
9. A titre de médicaments, les produits tels que définis à l'une quelconque des revendications 2 à 5 ainsi que leurs sels d'acides, pharmaceutiquement acceptables.
10. Compositions pharmaceutiques contenant, à titre de principe actif, au moins un médicament selon l'une des revendications 8 ou 9.
11. A titre de produits industriels, les produits de formule (IV) et les produits de formule (V) dans laquelle  $R_a$  représente un groupement protecteur du radical amino, les formules (IV) et (V) étant telles que définies à la revendication 6.

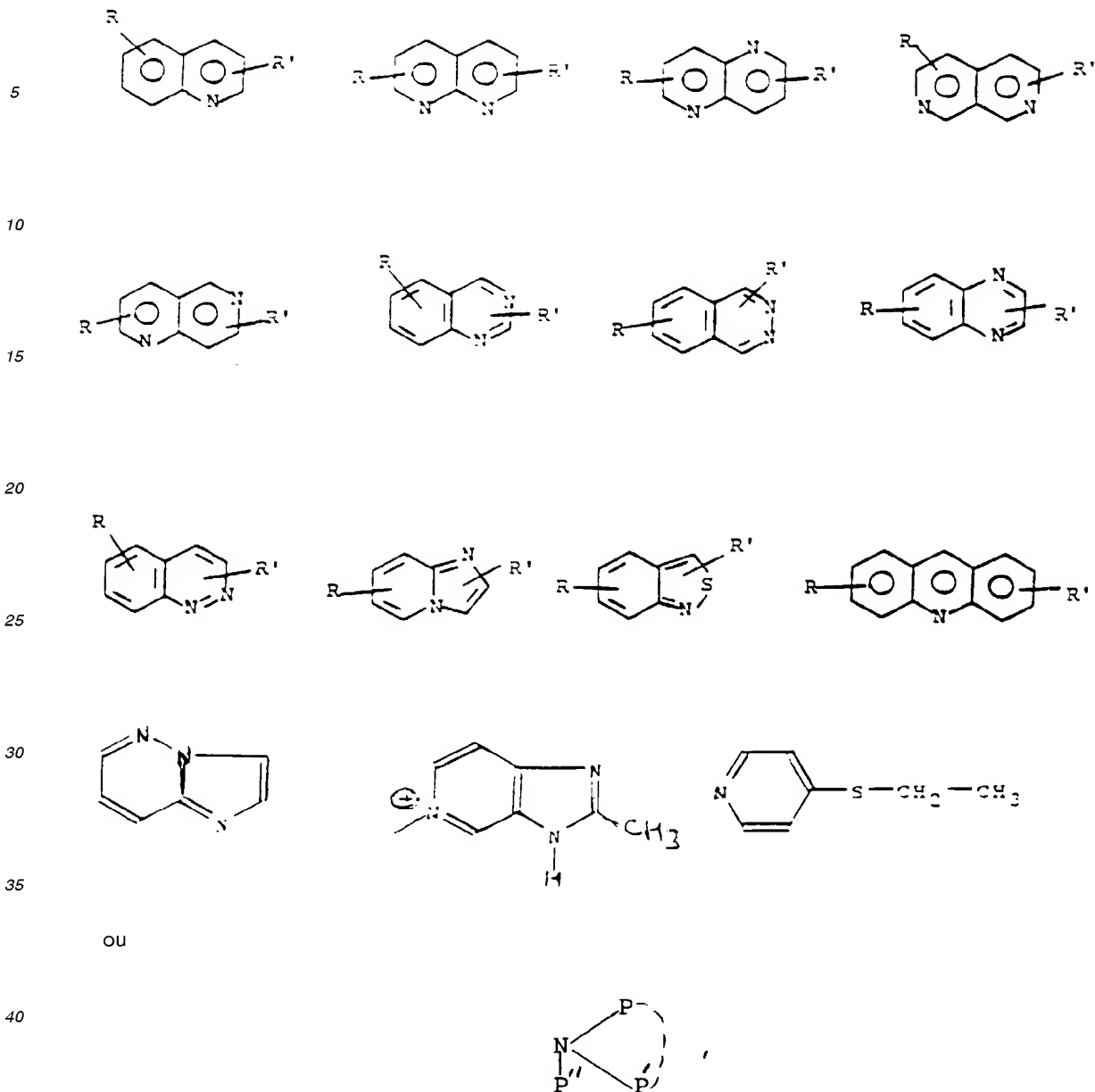
#### Revendications pour l'Etat contractant suivant : ES

1. Procédé pour préparer les produits de formule générale (I)

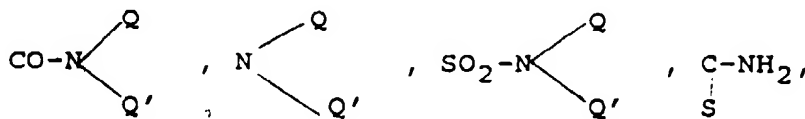


isomère syn, sous forme R ou S ou d'un mélange R, S, formule dans laquelle :  
 $R_1$  représente un radical choisi parmi les radicaux suivants :





sous forme d'ammonium quaternaire, l'expression sous forme d'ammonium quaternaire indiquant que le radical  $R_1$  est lié avec le groupement  $-\text{CH}=\text{CH}-\text{CH}_2-$  par le ou l'un des atomes d'azote qu'il comporte, dans lesquels R et R' identiques ou différents représentent un atome d'hydrogène, un radical alkyle renfermant de 1 à 4 atomes de carbone, un radical alcoxy renfermant de 1 à 4 atomes de carbone, un atome d'halogène, un radical  $\text{CO}_2\text{-Q}$ ,

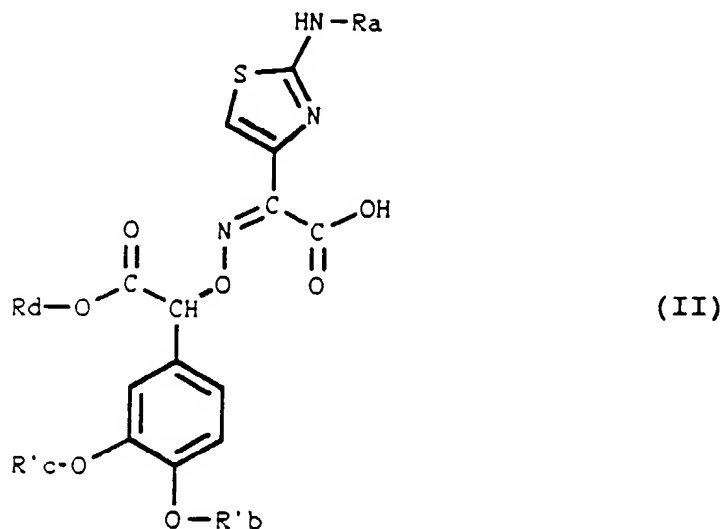


$\text{NH}-\text{CO}-\text{Q}$ ,  $\text{CN}$ ,  $\text{CH}_2-\text{CN}$ ,  $\text{CH}_2-\text{SQ}$  dans lesquels Q et Q' identiques ou différents représentent un atome d'hydrogène ou un radical alkyle renfermant de 1 à 4 atomes de carbone, P, P' et P'' identiques ou différents représentent

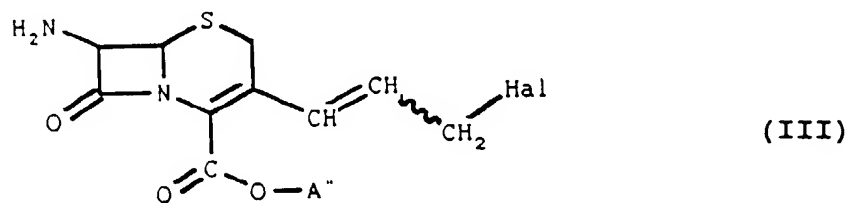
un radical alkyle renfermant au plus 4 atomes de carbone, éventuellement substitué par un des substituants indiqués ci-dessus pour R et R', le symbole } indiquant que P et P' peuvent éventuellement former avec l'atome d'azote auquel ils sont liés, un hétérocycle à 5 ou 6 chaînons.

R<sub>b</sub> et R<sub>c</sub>, identiques ou différents représentent un atome d'hydrogène ou un groupement acyle, choisi parmi les radicaux acétyle, propionyle et benzoyle,

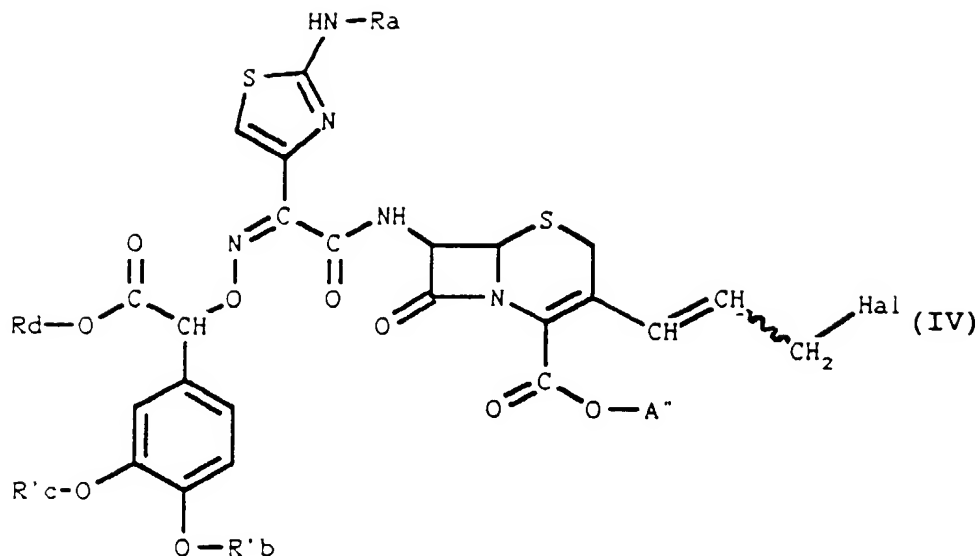
A et A' identiques ou différents représentent un atome d'hydrogène, un équivalent de métal alcalin, alcalino-terreux, de magnésium, d'ammonium ou d'une base organique aminée ou A et A' représentent le reste d'un groupement ester facilement clivable ou CO<sub>2</sub>A représente CO<sub>2</sub>; le trait ondulé signifie que le groupement CH<sub>2</sub>R<sub>1</sub> peut se trouver dans la position E ou Z ainsi que les sels des produits de formule (I) avec les acides minéraux ou organiques, caractérisé en ce que l'on fait agir un produit de formule (II) :



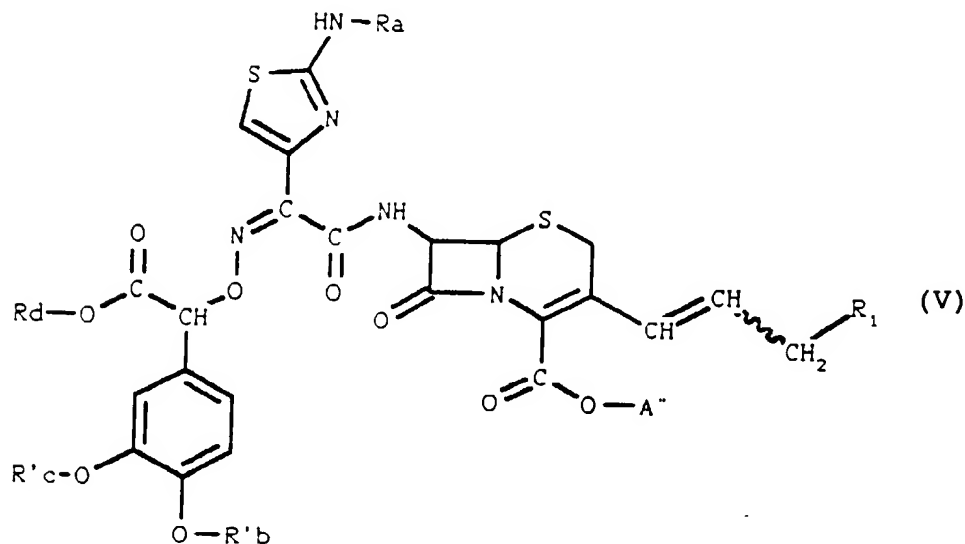
isomère syn, racémique ou optiquement actif ou un dérivé fonctionnel du produit de formule (II), dans laquelle R<sub>a</sub> représente un atome d'hydrogène ou un groupement protecteur du radical amino, R<sub>b</sub> et R<sub>c</sub> identiques ou différents représentent un atome d'hydrogène ou un groupement protecteur du radical hydroxyle, R<sub>d</sub> représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable, avec un produit de formule (III) :



dans laquelle Hal représente un atome d'halogène, A'' représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable et le trait ondulé signifie que le groupement CH<sub>2</sub>Hal peut se trouver dans la position E ou Z pour obtenir un produit de formule (IV) :



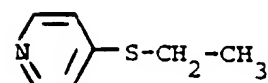
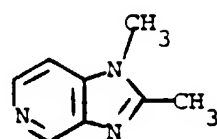
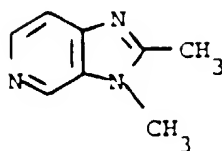
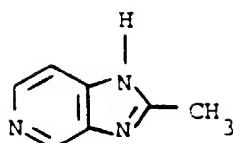
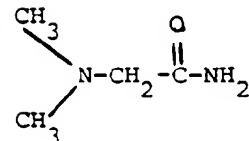
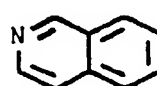
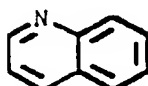
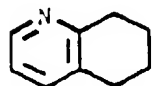
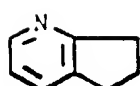
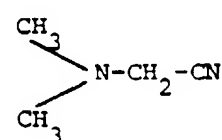
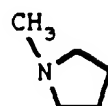
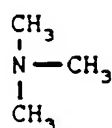
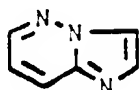
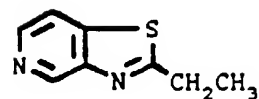
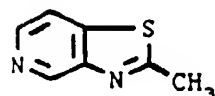
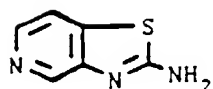
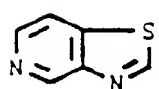
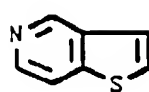
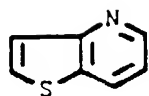
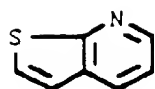
que l'on fait agir avec un réactif capable d'introduire le radical  $\text{R}_1$  pour obtenir un produit de formule (V) :



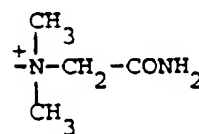
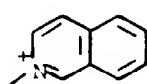
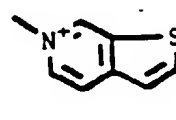
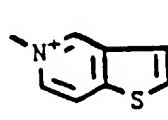
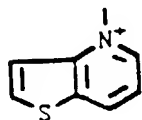
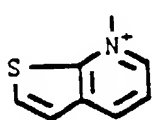
que, si désiré, l'on sépare en ses isomères E ou Z ou transforme les isomères Z en isomères E et produits de formule (v) que, si nécessaire ou si désiré, l'on soumet à une ou plusieurs des réactions suivantes, dans un ordre quelconque : a) coupure par hydrolyse ou par action de la thiourée de tout ou partie des groupements esters ou des groupements de protection du radical amino ou des radicaux hydroxyles,

- b) estérification ou salification par une base du ou des radicaux carboxyliques,  
 c) salification par un acide du radical amino,  
 d) séparation des produits sous forme de mélange R,S en R ou S.

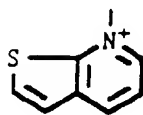
2. Procédé de préparation selon la revendication 1 caractérisé en ce que le réactif capable d'introduire le radical  $\text{R}_1$  est choisi parmi les réactifs de formule :



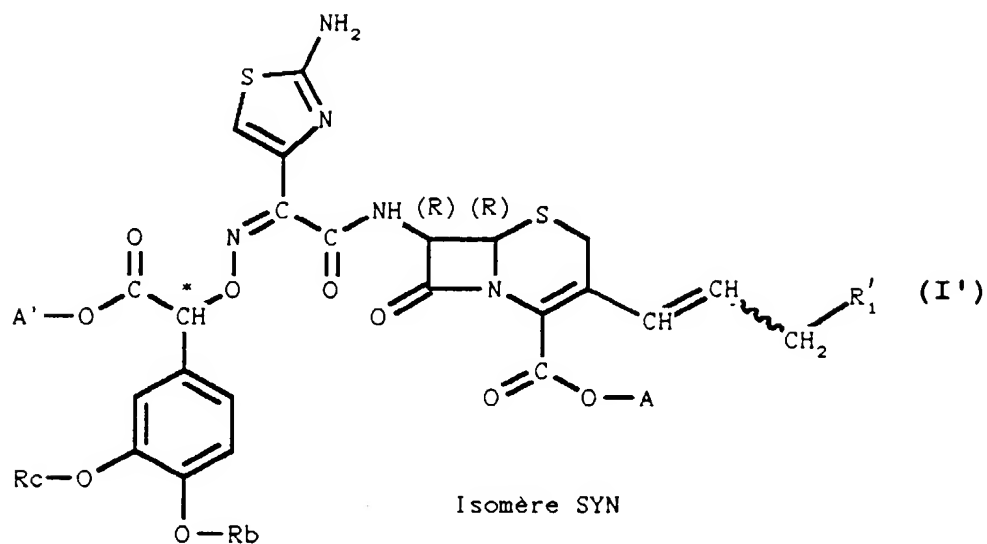
3. Procédé de préparation selon la revendication 1 ou 2, caractérisé en ce que le réactif capable d'introduire le radical  $R_1$  est choisi parmi les réactifs :



de préférence :

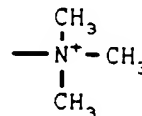
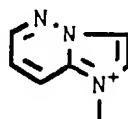
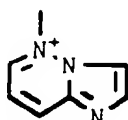
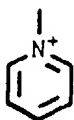
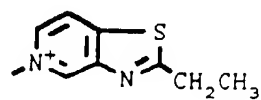
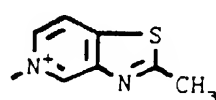
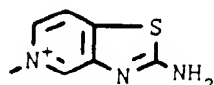
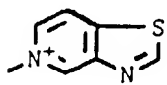
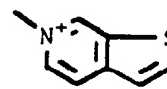
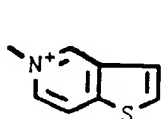
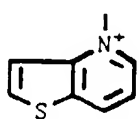
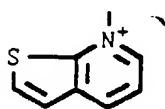


4. Procédé selon la revendication 1 pour la préparation des produits de formule (I) telle que définie à la revendication 1 répondant à la formule (I') :

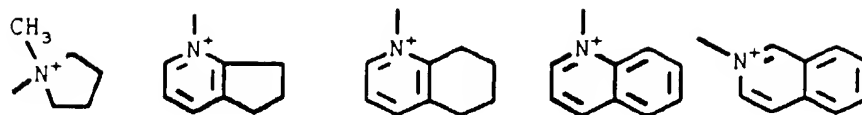


isomère syn, sous forme R ou S ou d'un mélange R, S, formule dans laquelle :

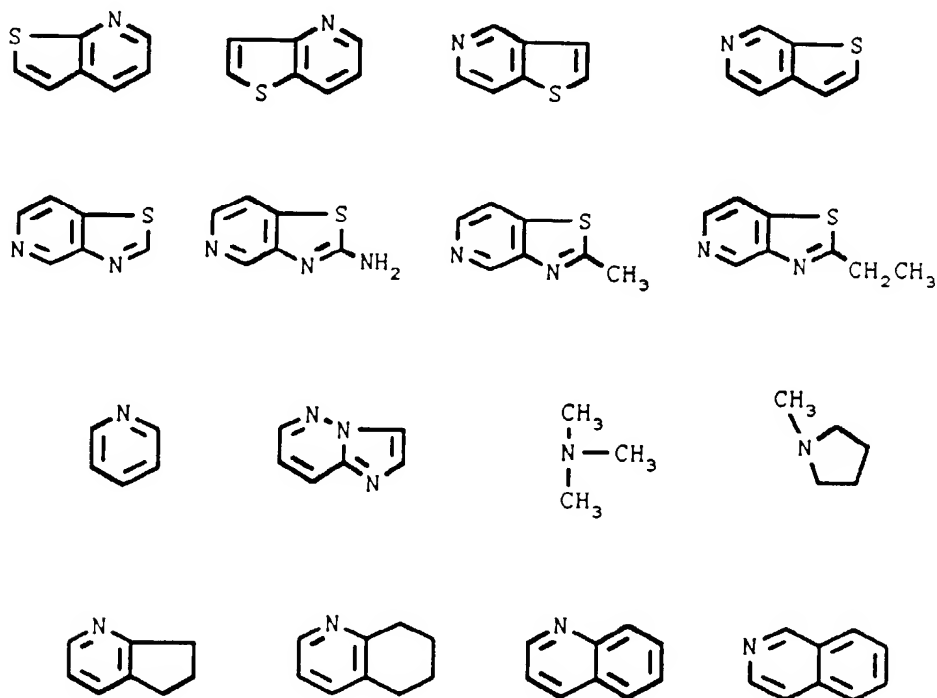
A, A', R<sub>b</sub> et R<sub>c</sub> conservent leur signification précédente et R'<sub>1</sub> représente un radical choisi parmi les radicaux suivants



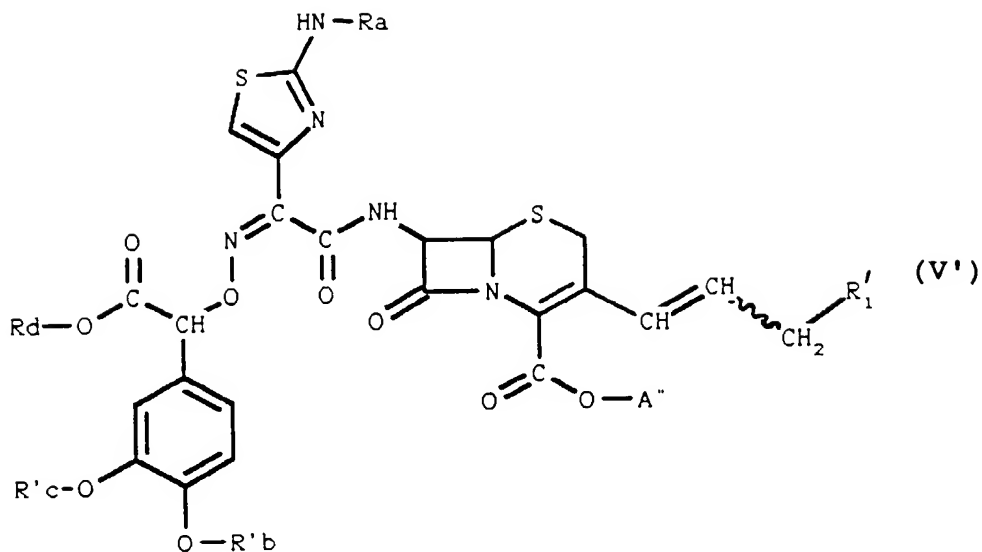




ainsi que les sels des produits de formule (I') avec les acides minéraux ou organiques, caractérisé en ce que l'on fait agir un produit de formule (II) sur un produit de formule (III) définis comme à la revendication 1 puis fait agir sur le produit de formule (IV) obtenu un réactif choisi parmi les réactifs de formule



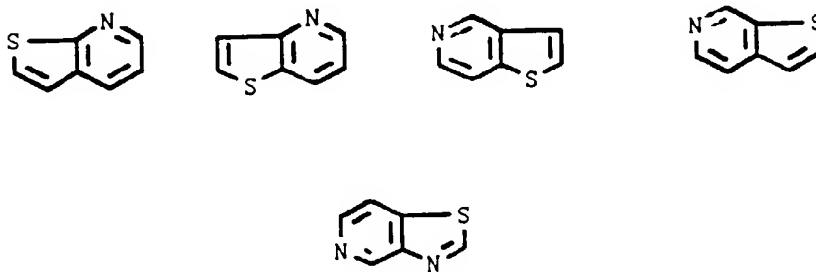
pour obtenir un produit de formule (V') :



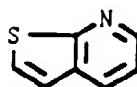
que, si désiré, l'on sépare en ses isomères E ou Z ou transforme les isomères Z en isomères E et produits de formule (V) que, si nécessaire ou si désiré, l'on soumet à une ou plusieurs des réactions suivantes, dans un ordre quelconque :

- 25
- a) coupure par hydrolyse ou par action de la thiourée de tout ou partie des groupements esters ou des groupements de protection du radical amino ou des radicaux hydroxyles,
- b) estérification ou salification par une base du ou des radicaux carboxyliques,
- 30 c) salification par un acide du radical amino,
- d) séparation des produits sous forme de mélange R,S en R ou S.

5. Procédé selon la revendication 4, caractérisé en ce que le réactif utilisé sur le produit de formule (IV) est choisi parmi les réactifs :

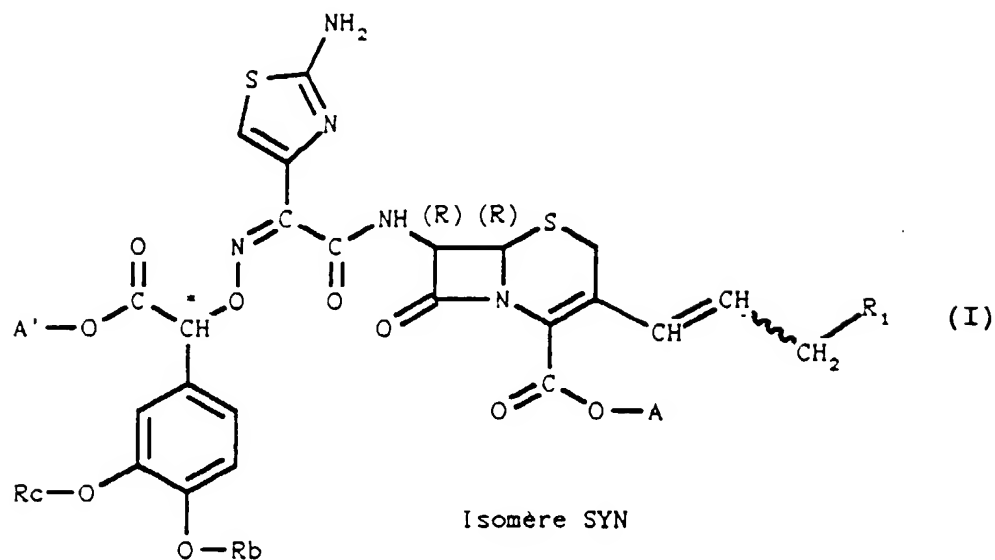


de préférence :



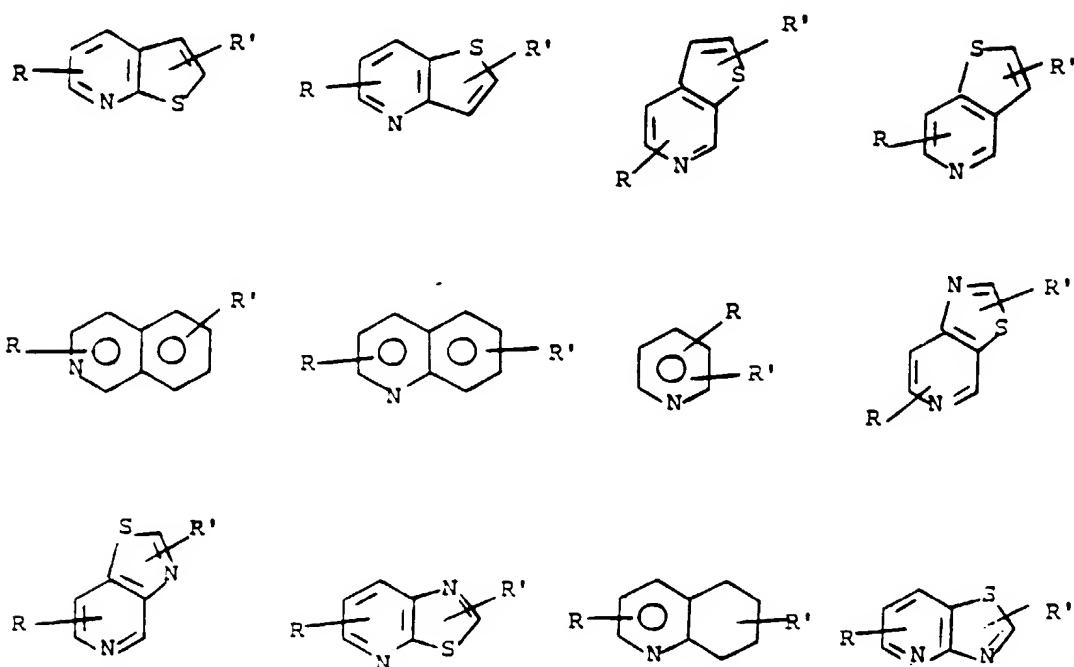
## Revendications pour l'Etat contractant suivant : GR

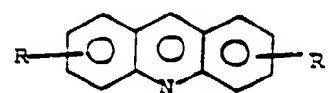
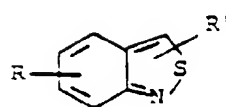
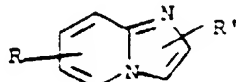
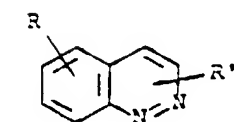
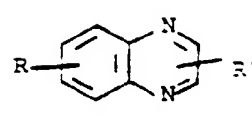
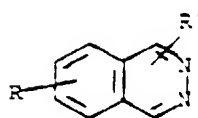
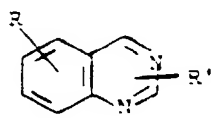
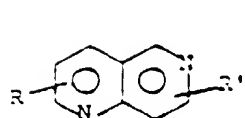
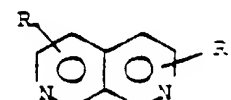
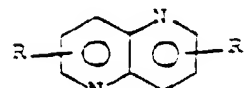
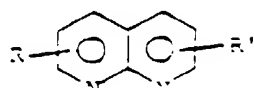
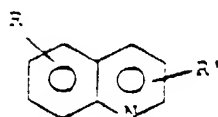
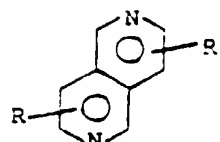
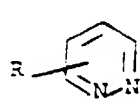
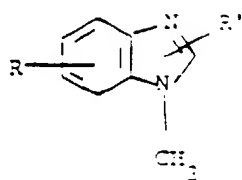
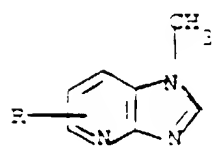
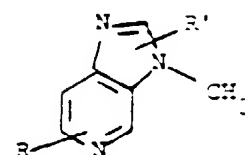
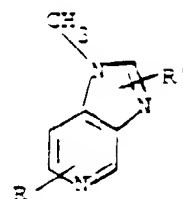
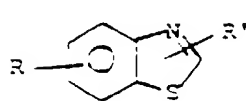
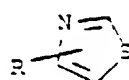
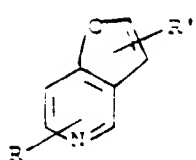
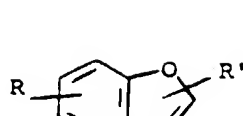
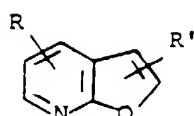
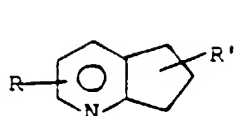
## 1. Procédé pour préparer les produits de formule générale (I) :

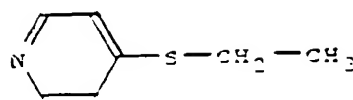
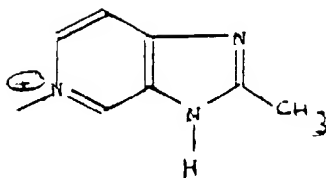
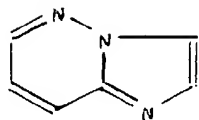


isomère syn, sous forme R ou S ou d'un mélange R, S, formule dans laquelle :

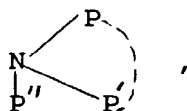
R<sub>1</sub> représente un radical choisi parmi les radicaux suivants :



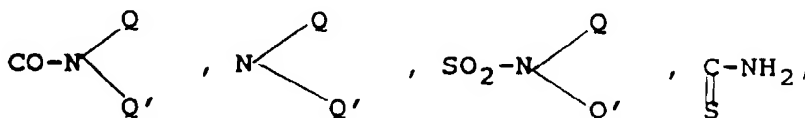




ou



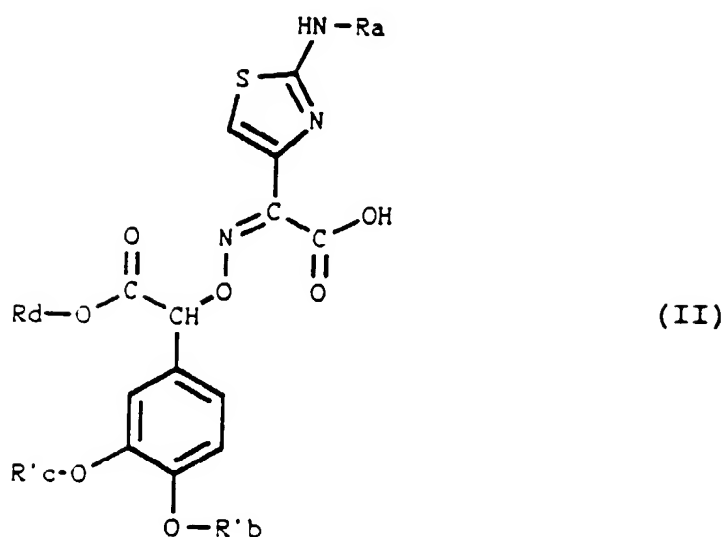
sous forme d'ammonium quaternaire, l'expression sous forme d'ammonium quaternaire indiquant que le radical  $R_1$  est lié avec le groupement  $-\text{CH}=\text{CH}-\text{CH}_2-$  par le ou l'un des atomes d'azote qu'il comporte, dans lesquels R et R' identiques ou différents représentent un atome d'hydrogène, un radical alkyle renfermant de 1 à 4 atomes de carbone, un radical alcoxy renfermant de 1 à 4 atomes de carbone, un atome d'halogène, un radical  $\text{CO}_2\text{-Q}$ ,



$\text{NH-CO-Q}$ ,  $\text{CN}$ ,  $\text{CH}_2\text{-CN}$ ,  $\text{CH}_2\text{-SQ}$  dans lesquels Q et Q' identiques ou différents représentent un atome d'hydrogène ou un radical alkyle renfermant de 1 à 4 atomes de carbone, P, P' et P'' identiques ou différents représentent un radical alkyle renfermant au plus 4 atomes de carbone, éventuellement substitué par un des substituants indiqués ci-dessus pour R et R', le symbole  $\text{P} \cdots \text{P}'$  indiquant que P et P' peuvent éventuellement former avec l'atome d'azote auquel ils sont liés, un hétérocycle à 5 ou 6 chaînons.

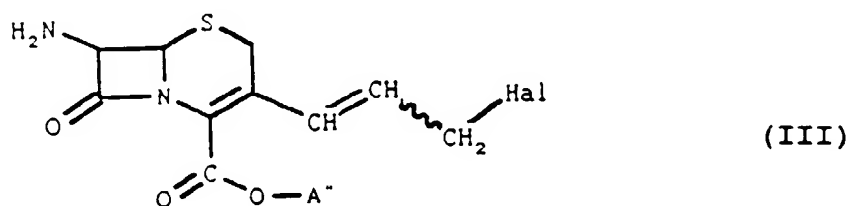
$R_b$  et  $R_c$ , identiques ou différents représentent un atome d'hydrogène ou un groupement acyle, choisi parmi les radicaux acétyle, propionyle et benzoyle,

A et A' identiques ou différents représentent un atome d'hydrogène, un équivalent de métal alcalin, alcalino-terreux, de magnésium, d'ammonium ou d'une base organique aminée ou A et A' représentent le reste d'un groupement ester facilement clivable ou  $\text{CO}_2\text{A}$  représente  $\text{CO}_2^-$ ; le trait ondulé signifie que le groupement  $\text{CH}_2\text{R}_1$  peut se trouver dans la position E ou Z ainsi que les sels des produits de formule (I) avec les acides minéraux ou organiques, caractérisé en ce que l'on fait agir un produit de formule (II) :



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isomère syn, racémique ou optiquement actif ou un dérivé fonctionnel du produit de formule (II), dans laquelle  $R_a$  représente un atome d'hydrogène ou un groupement protecteur du radical amino,  $R'_b$  et  $R'_c$  identiques ou différents représentent un atome d'hydrogène ou un groupement protecteur du radical hydroxyle,  $R_d$  représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable, avec un produit de formule (III) :



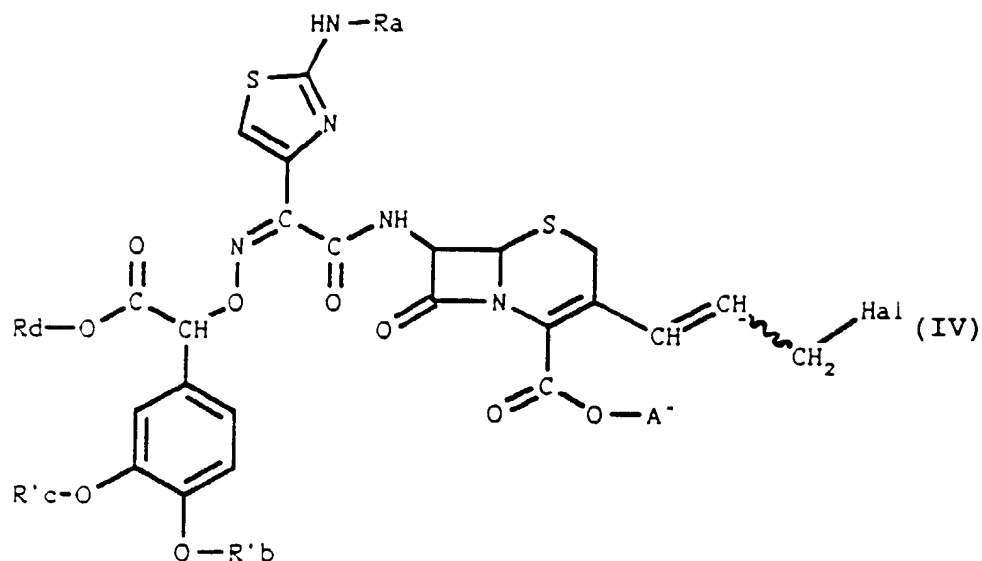
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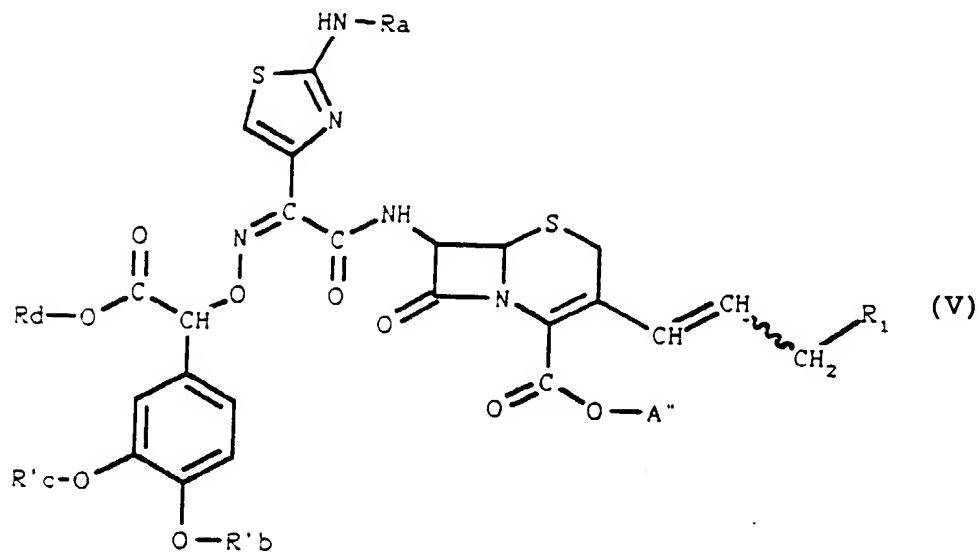
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dans laquelle Hal représente un atome d'halogène,  $A''$  représente un atome d'hydrogène ou le reste d'un groupement ester facilement éliminable et le trait ondulé signifie que le groupement  $CH_2Hal$  peut se trouver dans la position E ou Z pour obtenir un produit de formule (IV) :



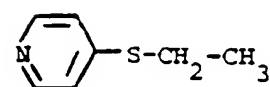
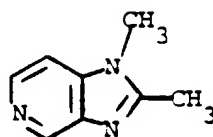
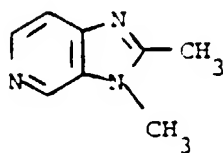
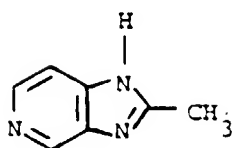
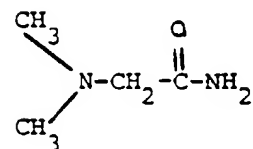
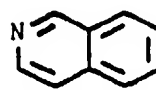
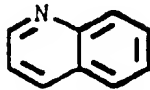
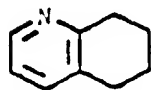
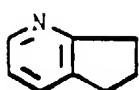
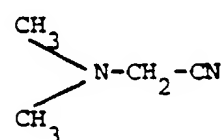
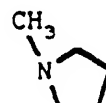
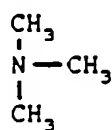
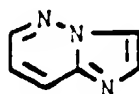
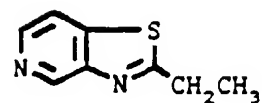
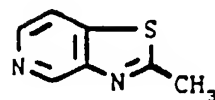
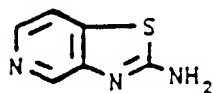
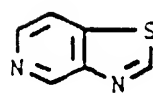
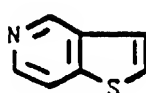
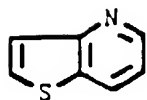
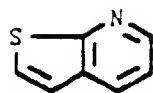
que l'on fait agir avec un réactif capable d'introduire le radical R<sub>1</sub> pour obtenir un produit de formule (V) :



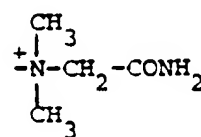
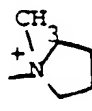
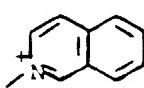
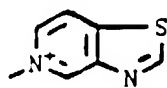
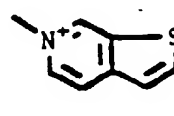
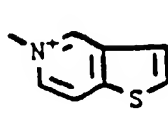
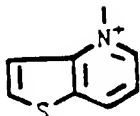
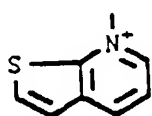
que, si désiré, l'on sépare en ses isomères E ou Z ou transforme les isomères Z en isomères E et produits de formule (V) que, si nécessaire ou si désiré, l'on soumet à une ou plusieurs des réactions suivantes, dans un ordre quelconque :

- a) coupure par hydrolyse ou par action de la thiourée de tout ou partie des groupements esters ou des groupements de protection du radical amino ou des radicaux hydroxyles,
- b) estérification ou salification par une base du ou des radicaux carboxyliques,
- c) salification par un acide du radical amino,
- d) séparation des produits sous forme de mélange R,S en R ou S.

2. Procédé de préparation selon la revendication 1 caractérisé en ce que le réactif capable d'introduire le radical R<sub>1</sub> est choisi parmi les réactifs de formule :

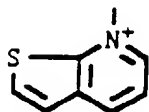


3. Procédé de préparation selon la revendication 1 ou 2, caractérisé en ce que le réactif capable d'introduire le radical  $R_1$  est choisi parmi les réactifs :

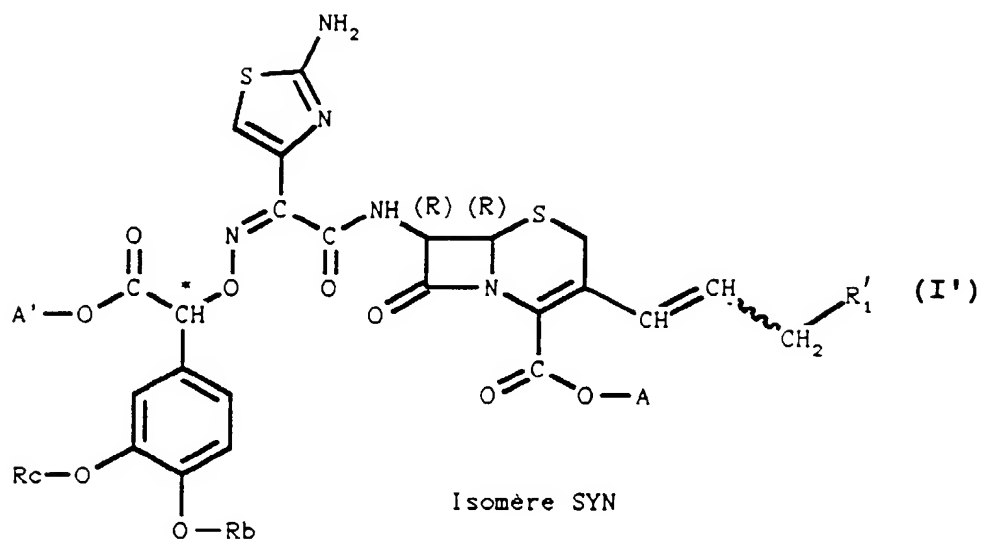


de préférence :



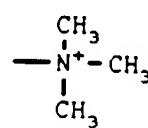
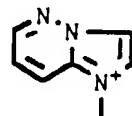
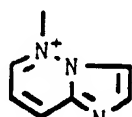
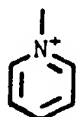
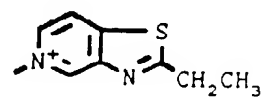
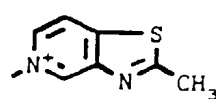
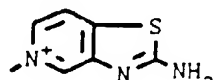
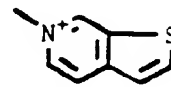
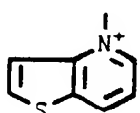
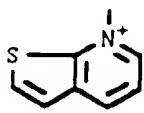


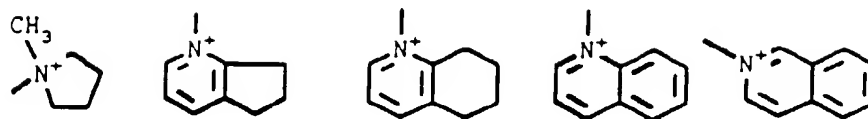
4. Procédé selon la revendication 1 pour la préparation des produits de formule (I) telle que définie à la revendication 1 répondant à la formule (I') :



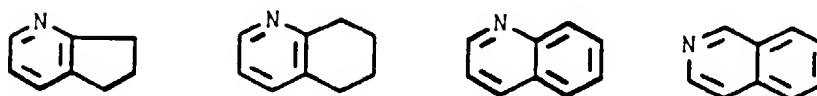
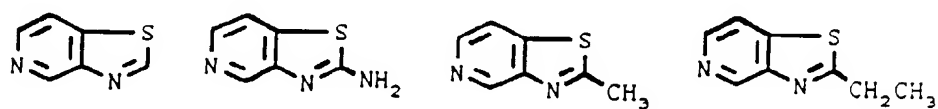
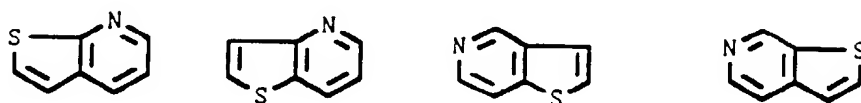
isomère syn, sous forme R ou S ou d'un mélange R, S, formule dans laquelle :

A, A', R<sub>b</sub> et R<sub>c</sub> conservent leur signification précédente et R'<sub>1</sub> représente un radical choisi parmi les radicaux suivants

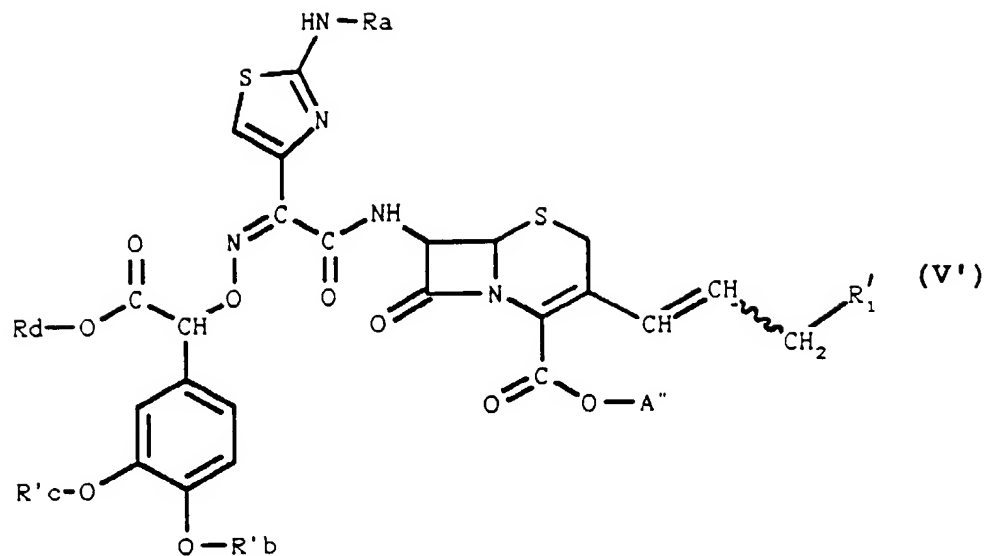




ainsi que les sels des produits de formule (I') avec les acides minéraux ou organiques, caractérisé en ce que l'on fait agir un produit de formule (II) sur un produit de formule (III) définis comme à la revendication 1 puis fait agir sur le produit de formule (IV) obtenu un réactif choisi parmi les réactifs de formule



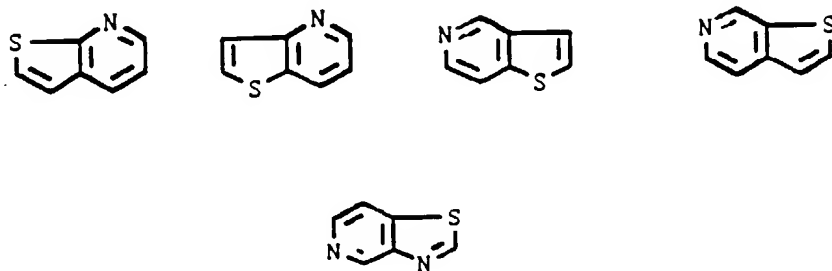
pour obtenir un produit de formule (V') :



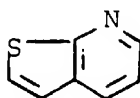
que, si désiré, l'on sépare en ses isomères E ou Z ou transforme les isomères Z en isomères E et produits de formule (V) que, si nécessaire ou si désiré, l'on soumet à une ou plusieurs des réactions suivantes, dans un ordre quelconque :

- a) coupure par hydrolyse ou par action de la thiourée de tout ou partie des groupements esters ou des groupements de protection du radical amino ou des radicaux hydroxyles,  
 b) estérification ou salification par une base du ou des radicaux carboxyliques,  
 c) salification par un acide du radical amino,  
 d) séparation des produits sous forme de mélange R,S en R ou S.

5. Procédé selon la revendication 4, caractérisé en ce que le réactif utilisé sur le produit de formule (IV) est choisi parmi les réactifs :



de préférence :



6. Procédé selon l'une quelconque des revendications 1 à 5, caractérisé en ce que les produits de départ et le réactif utilisés sont choisis de manière telle que l'on prépare :

- le [6R-[3(E), 6alpha, 7bêta(Z)]] 5-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiazolo[4,5-c] pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 7-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] thiéno[2,3-b] pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables et particulièrement sous forme S,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 2-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] isoquinoléinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 1-méthyl pyrrolidinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] 1-[3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propényl] 6,7-dihydro 5H-pyridinium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables,
- le [6R-[3(E), 6alpha, 7bêta(Z)]] N-(2-amino 2-oxoéthyl) 3-[7-[(2-amino 4-thiazolyl) [[1-(3,4-dihydroxyphényl) 2-hydroxy 2-oxoéthoxy] imino] acétyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-diméthyl 2-propèn-1-aminium sous forme R ou S ou d'un mélange R,S et sous forme de sel interne ou de sel avec les métaux alcalins, alcalino-terreux, le magnésium, l'ammoniaque, les bases organiques aminées, les acides et ses esters facilement clivables.

7. Procédé de préparation de compositions pharmaceutiques caractérisé en ce que l'on met à titre de principe actif l'un au moins des dérivés de formule (I) tels que définis à la revendication 1 ainsi que leurs sels d'acides pharmaceutiquement acceptables, sous une forme destinée à cet usage.

8. Procédé de préparation de compositions pharmaceutiques caractérisé en ce que l'on met à titre de principe actif l'un au moins des dérivés de formule (I') tels que définis à la revendication 4 ainsi que leurs sels d'acides pharmaceutiquement acceptables, sous une forme destinée à cet usage.

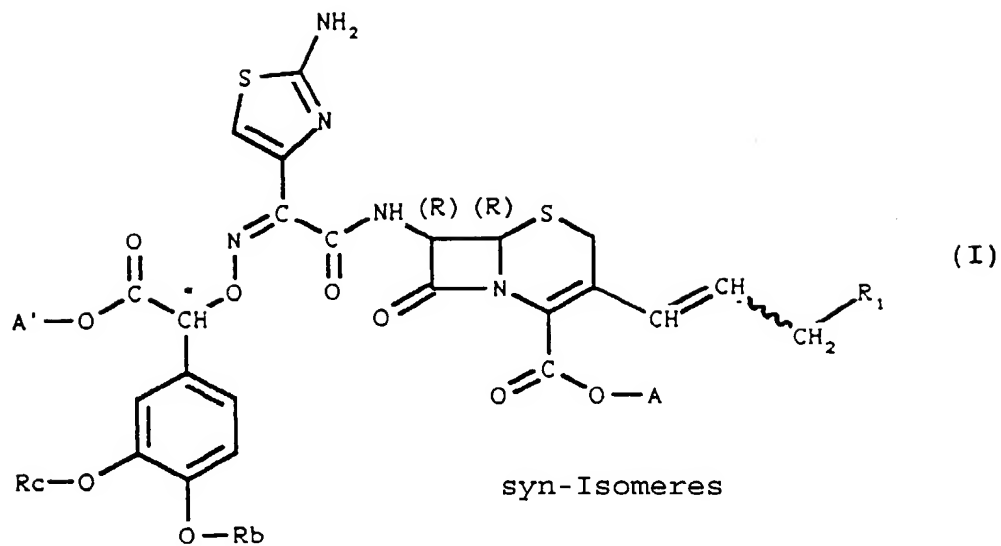
9. Procédé de préparation de compositions pharmaceutiques caractérisé en ce que l'on met à titre de principe actif l'un au moins des dérivés de formule (I) tels que définis à la revendication 6 ainsi que leurs sels d'acides pharmaceutiquement acceptables, sous une forme destinée à cet usage.

10. A titre de produits industriels, les produits de formule (IV) et les produits de formule (V) dans laquelle  $R_a$  représente un groupement protecteur du radical amino, les formules (IV) et (V) étant telles que définies à la revendication 5.

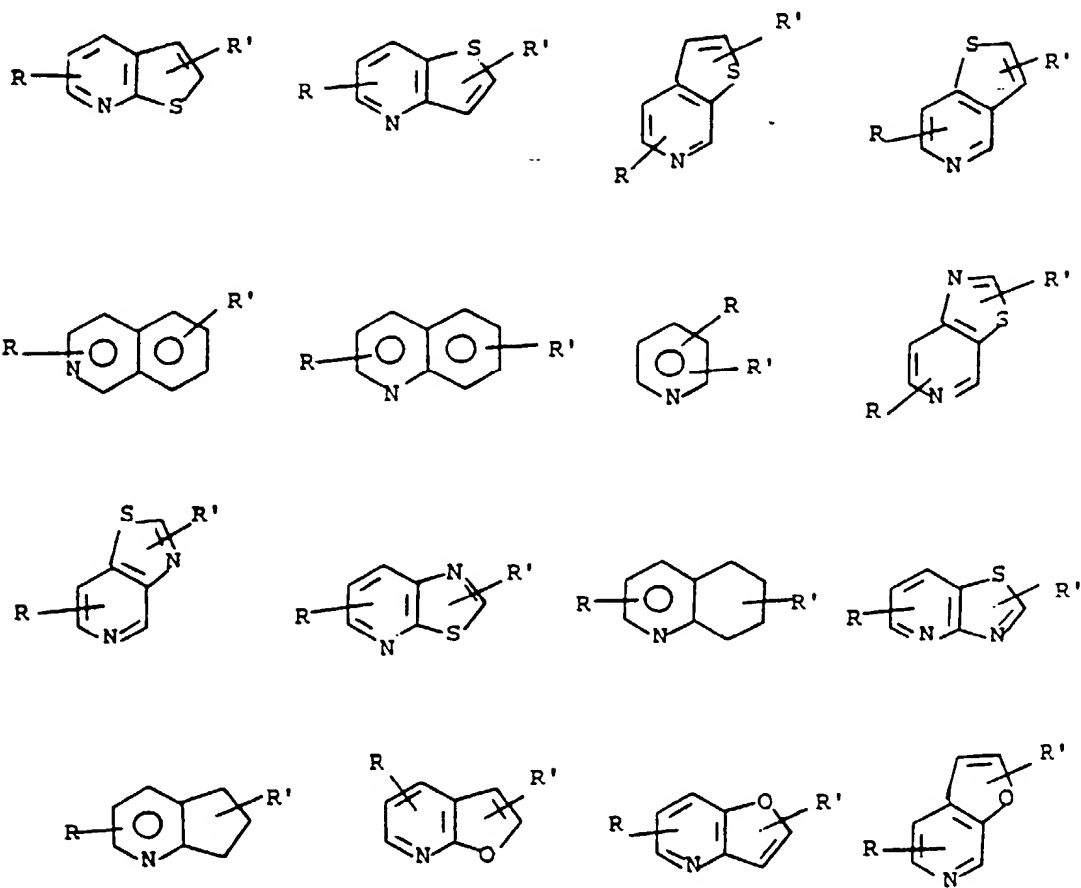
## Patentansprüche

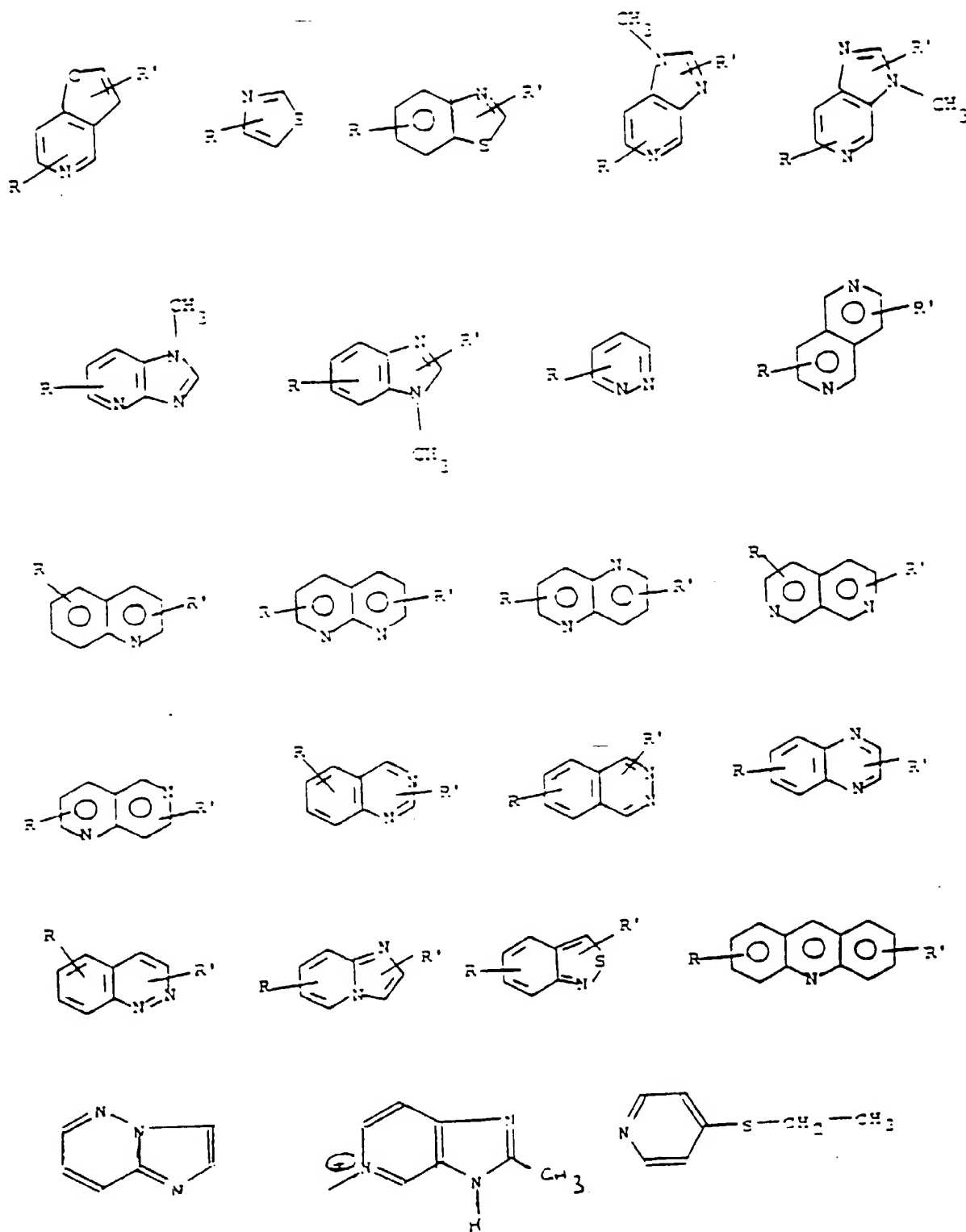
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindungen der allgemeinen Formel (I) :

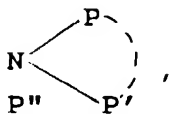


syn-Isomeres, in der R- oder S-Form oder in Form eines R,S-Gemisches, wobei in der Formel:  
 $R_1$  einen unter folgenden Resten ausgewählten Rest bedeutet:



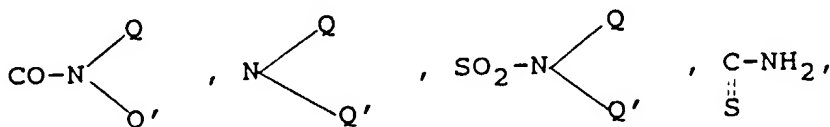


oder



in der Form von quaternärem Ammonium, wobei der Ausdruck "in der Form von quaternärem Ammonium" bedeutet, daß der Rest  $R_1$  mit der Gruppe  $-\text{CH}=\text{CH}-\text{CH}_2-$  über das Stickstoffatom oder über eines der Stickstoffatome, die er aufweist, gebunden ist,

worin R und R' gleich oder verschieden sind und ein Wasserstoffatom, einen Alkylrest mit 1 bis 4 Kohlenstoffatomen, einen Alkoxyrest mit 1 bis 4 Kohlenstoffatomen, ein Halogenatom, einen Rest der Formeln  $\text{CO}_2-\text{Q}$ ,



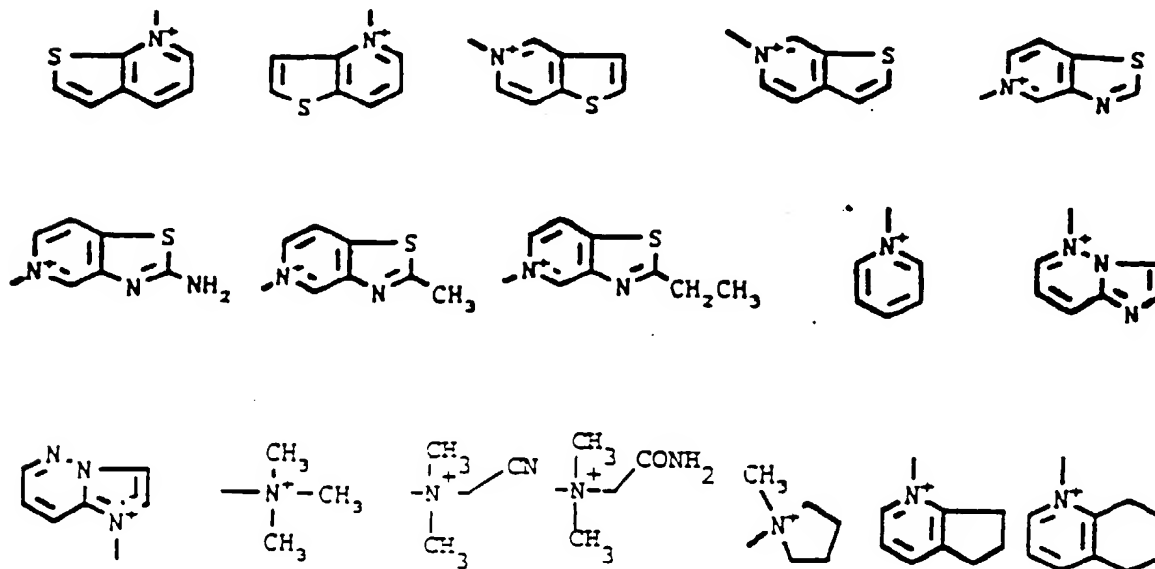
$\text{NH}-\text{CO}-\text{Q}$ ,  $\text{CN}$ ,  $\text{CH}_2-\text{CN}$  und  $\text{CH}_2-\text{SQ}$  bedeuten, wobei Q und Q' gleich oder verschieden sind und ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeuten, P, P' und P'' gleich oder verschieden sind und einen Alkylrest mit höchstens 4 Kohlenstoffatomen bedeuten, der ggf. durch einen der vorstehend für R und R' angegebenen Substituenten substituiert ist, wobei das Symbol  $\text{S}$  angibt, daß P und P' ggf. mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocyclus mit 5 oder 6 Kettengliedern bilden können,

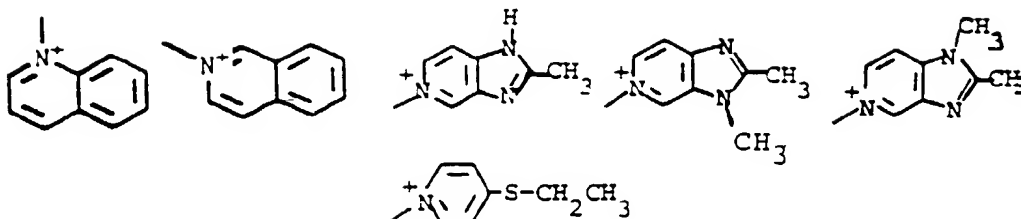
$R_b$  und  $R_c$  gleich oder verschieden sind und ein Wasserstoffatom oder eine Acylgruppe bedeuten, die unter Acetyl-, Propionyl- und Benzoylresten ausgewählt ist,

A und A' gleich oder verschieden sind und ein Wasserstoffatom, ein Äquivalent eines Alkalimetalls, Erdalkalimetalls, von Magnesium, Ammonium oder einer organischen Aminbase bedeutet oder A und A' den Rest einer leicht spaltbaren Estergruppe bedeutet oder  $\text{CO}_2\text{A}$  die Bedeutung  $\text{CO}_2^-$  hat; wobei die Wellenlinie bedeutet, daß die Gruppe  $\text{CH}_2\text{R}_1$  sich in der E- oder Z-Stellung befinden kann,

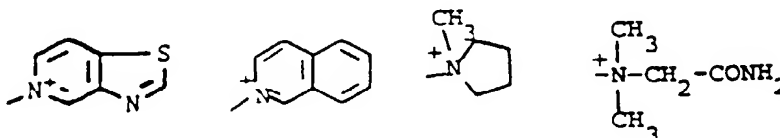
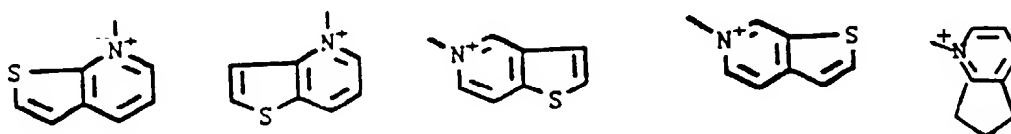
sowie die Salze der Verbindungen der Formel (I) mit anorganischen oder organischen Säuren.

2. Verbindungen der allgemeinen Formel (I) gemäß der Definitionen in Anspruch 1, wobei  $R_1$  unter folgenden Resten ausgewählt ist:

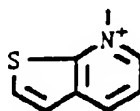




3. Verbindungen der allgemeinen Formel (I) gemäß der Definition in Anspruch 1 oder 2, wobei  $R_1$  unter folgenden Resten ausgewählt ist:



4. Verbindungen der allgemeinen Formel (I) gemäß der Definition in Anspruch 3, wobei  $R_1$  den folgenden Rest bedeutet:



5. Verbindungen der allgemeinen Formel (I) nach Anspruch 1 mit folgenden Bezeichnungen:

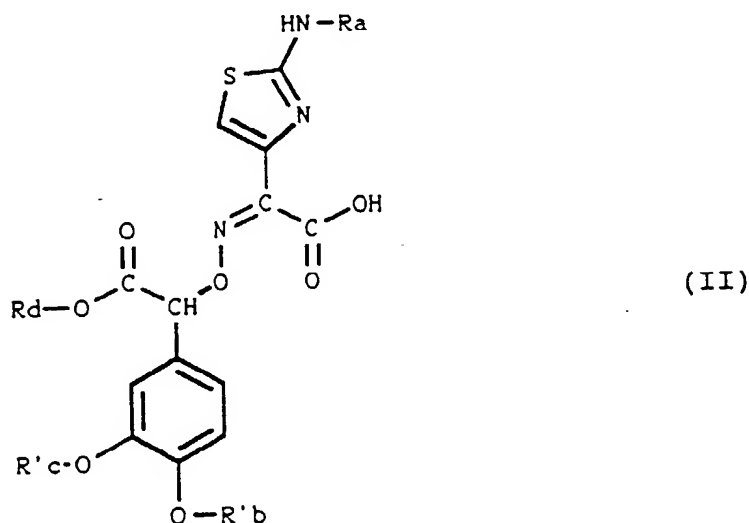
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-5-[3-[7-[(2-Amino-4-thiazolyl)][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thiazolo[4,5-c]pyridinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon,
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-7-[3-[7-[(2-Amino-4-thiazolyl)][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno[2,3-b]pyridinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon und insbesondere in der S-Form,
- [6R-(3(E),6 $\alpha$ ,7 $\beta$ (Z))]-2-[3-[7-[(2-Amino-4-thiazolyl)][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-isochinolinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon,
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-1-[3-[7-[(2-Amino-4-thiazolyl)][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-1-methylpyrrolidinium in



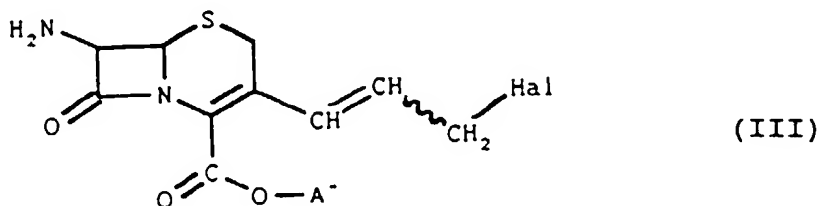
der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon,

- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-1-(3-[7-[(2-Amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl)-6,7-dihydro-5H-pyridinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon und
- [6R[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-N-(2-Amino-2-oxoethyl)-3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon.

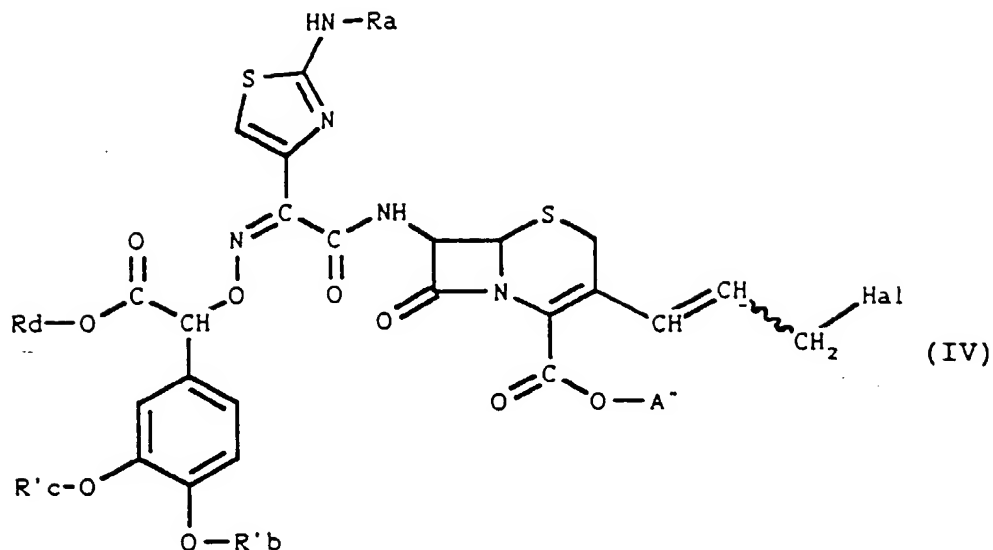
6. Verfahren zur Herstellung der Verbindung in der Formel (I) gemäß der Definition in Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formel (II)



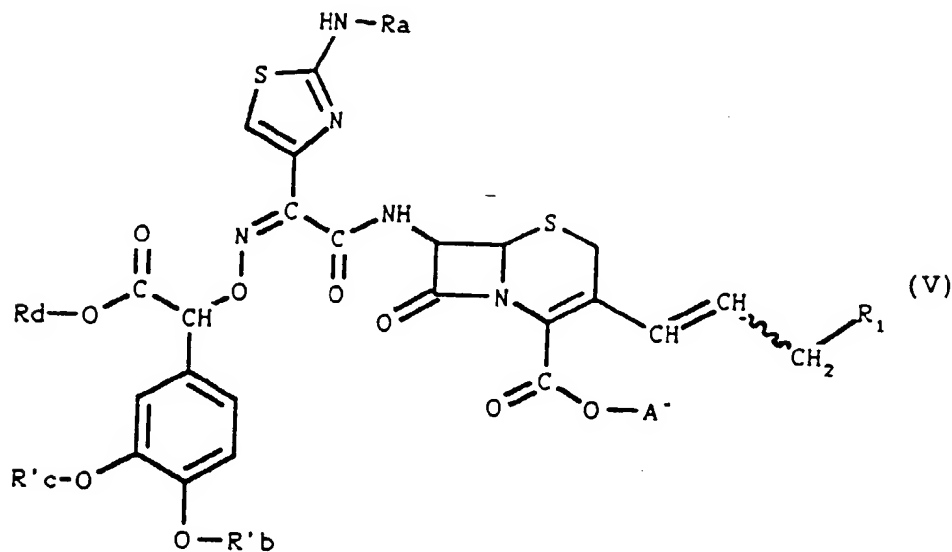
syn-Isomeres, racemisch oder optisch aktiv oder ein funktionelles Derivat der Verbindung der Formel (II), wobei  $R_a$  ein Wasserstoffatom oder eine Aminoschutzgruppe bedeutet,  $R'_b$  und  $R'_c$  gleich oder verschieden sind und ein Wasserstoffatom oder eine Hydroxylschutzgruppe bedeuten,  $R_d$  ein Wasserstoffatom oder den Rest einer leicht zu beseitigenden Estergruppe bedeutet, mit einer Verbindung der Formel (III) umgesetzt:



worin Hal ein Halogenatom bedeutet,  $A^-$  ein Wasserstoffatom oder den Rest einer leicht zu beseitigenden Estergruppe bedeutet und die Wellenlinie bedeutet, daß die  $CH_2Hal$ -Gruppe sich in der E- oder Z-Stellung befinden kann, wodurch man eine Verbindung der Formel (IV) erhält:



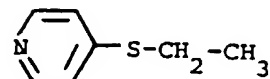
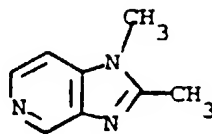
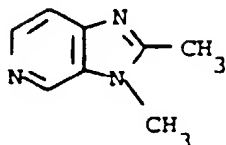
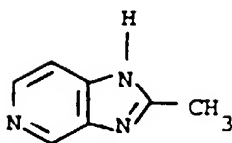
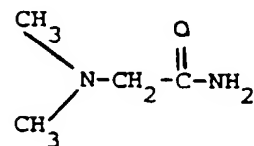
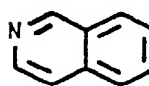
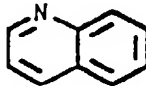
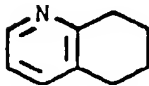
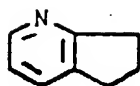
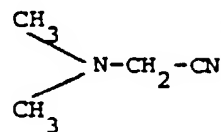
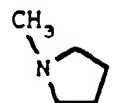
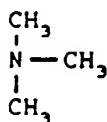
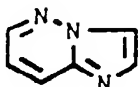
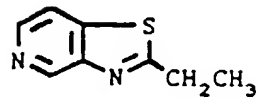
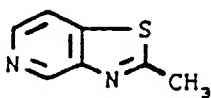
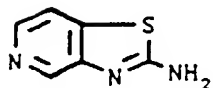
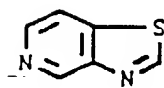
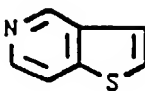
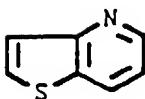
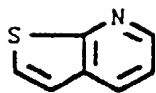
25 die man mit einem Reagenz, das zur Einführung des Restes  $R_1$  befähigt ist, umsetzt, wodurch man eine Verbindung der Formel (V) erhält:



50 die man ggf. in ihre E- oder Z-Isomeren auftrennt, oder die Z-Isomeren in E-Isomere umwandelt, wobei man ggf. die Verbindungen der Formel (V) einer oder mehreren der folgenden Reaktionen in einer beliebigen Reihenfolge unterwirft:

- 55
- a) Abspalten der Gesamtheit oder eines Teils der Estergruppen, der Aminoschutzgruppen oder der Hydroxylschutzgruppen durch Hydrolyse oder durch Einwirkung von Thioharnstoff,
  - b) Veresterung oder Salzbildung des oder der Carboxylreste mit einer Base,
  - c) Salzbildung des Aminorestes mit einer Säure und
  - d) Auftrennung der Produkte in Form des R,S-Gemisches in die R- oder S-Form.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß das Reagenz, das zur Einführung des Restes  $R_1$  befähigt ist, unter folgenden Reagenzien ausgewählt ist:



8. Verbindungen der Formel (I) gemäß der Definition in Anspruch 1 sowie deren pharmazeutisch verträgliche Salze mit Säuren als Arzneistoffe.

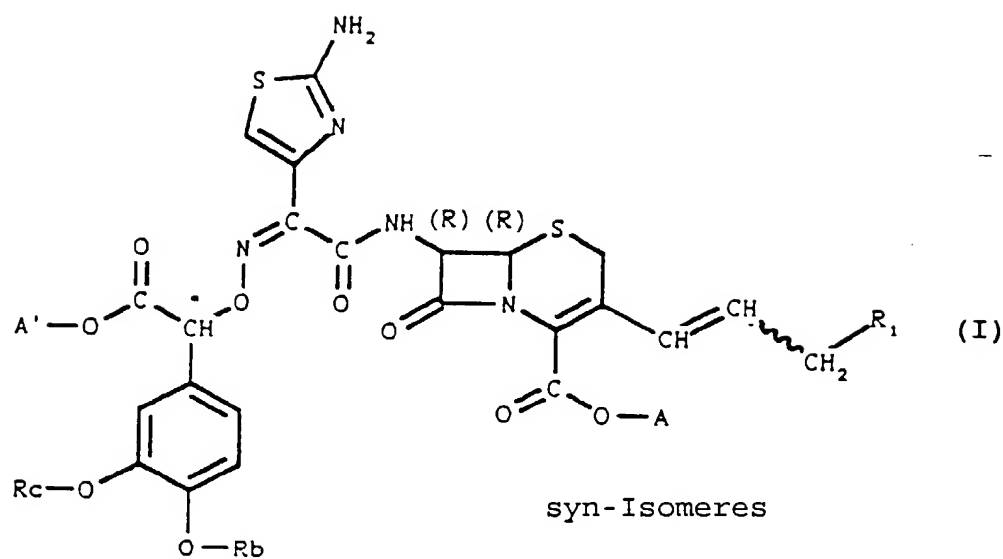
9. Verbindungen nach einem der Ansprüche 2 bis 5 sowie deren pharmazeutisch verträgliche Salze als Arzneistoffe.

10. Pharmazeutische Zusammensetzungen, enthaltend als Wirkstoff mindestens einen Arzneistoff nach einem der Ansprüche 8 oder 9.

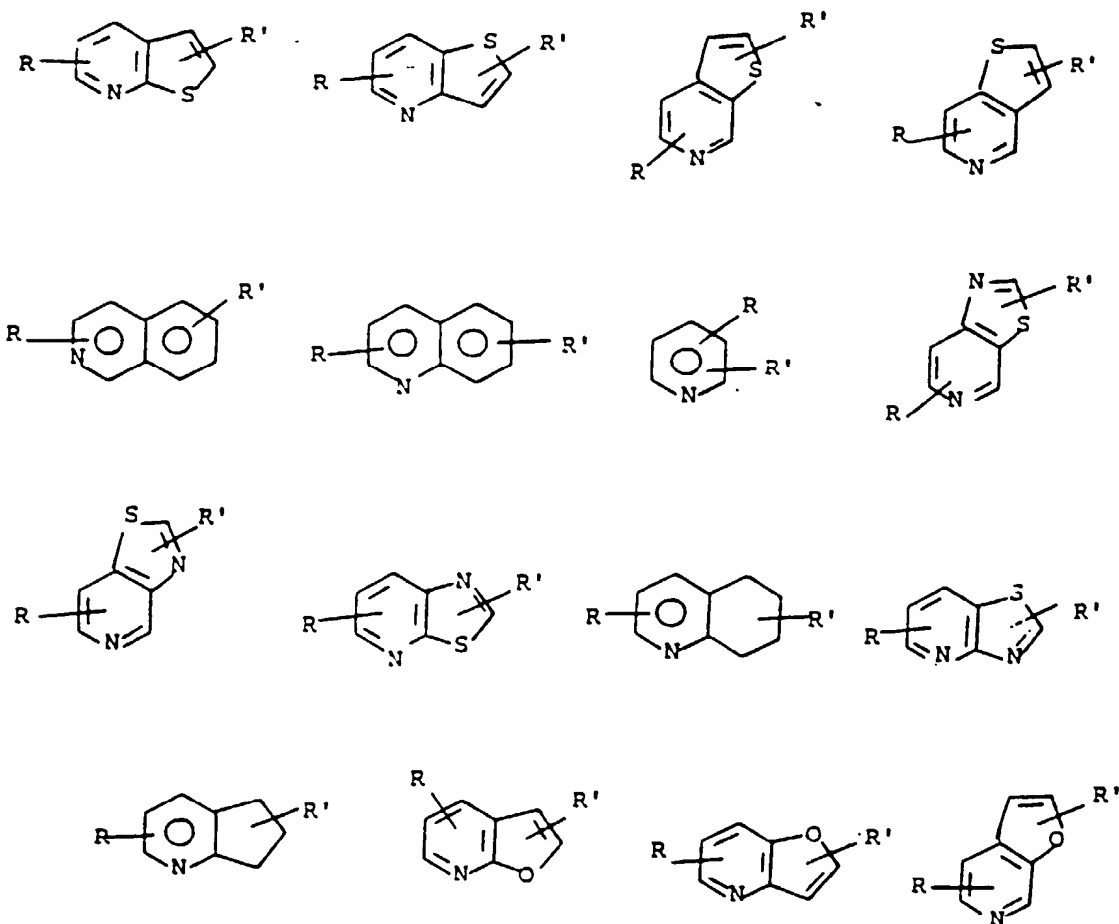
11. Verbindungen der Formel (IV) und Verbindungen der Formel (V), worin  $R_a$  eine Aminoschutzgruppe bedeutet, wobei die Formeln (IV) und (V) der Definition in Anspruch 6 entsprechen, als gewerblich einzusetzende Verbindungen.

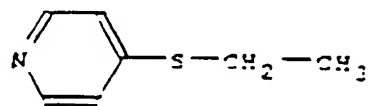
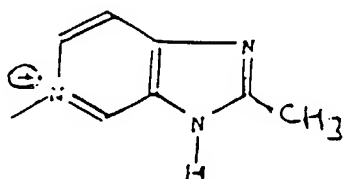
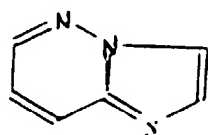
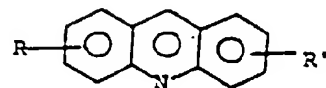
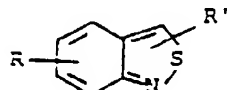
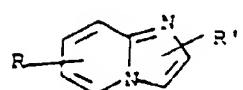
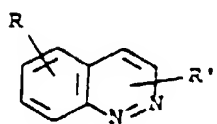
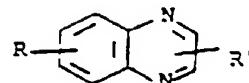
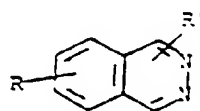
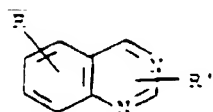
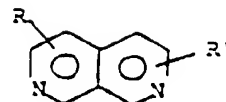
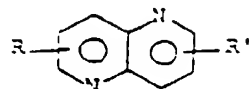
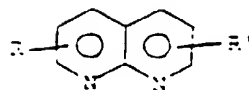
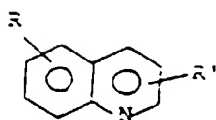
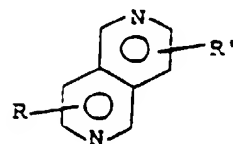
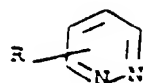
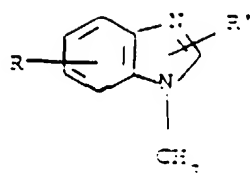
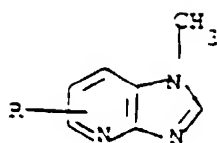
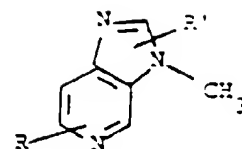
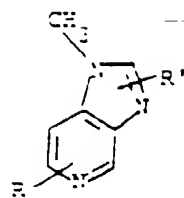
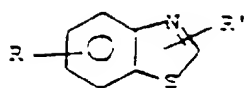
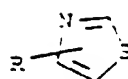
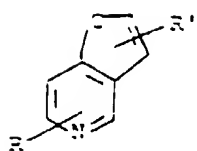
#### Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung der Verbindungen der allgemeinen Formel (I) :

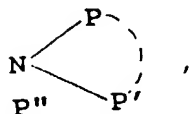


syn-Isomeres, in der R- oder S-Form oder in Form eines R,S-Gemisches, wobei in der Formel:  
 $R_1$  einen unter folgenden Resten ausgewählten Rest bedeutet:



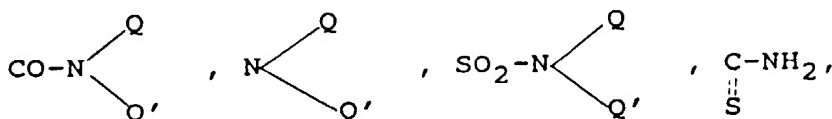


oder



in der Form von quaternärem Ammonium, wobei der Ausdruck "in der Form von quaternärem Ammonium" bedeutet, daß der Rest  $R_1$  mit der Gruppe  $-\text{CH}=\text{CH}-\text{CH}_2-$  über das Stickstoffatom oder über eines der Stickstoffatome, die er aufweist, gebunden ist,

worin R und R' gleich oder verschieden sind und ein Wasserstoffatom, einen Alkylrest mit 1 bis 4 Kohlenstoffatomen, einen Alkoxyrest mit 1 bis 4 Kohlenstoffatomen, ein Halogenatom, einen Rest der Formeln  $\text{CO}_2-\text{Q}$ ,

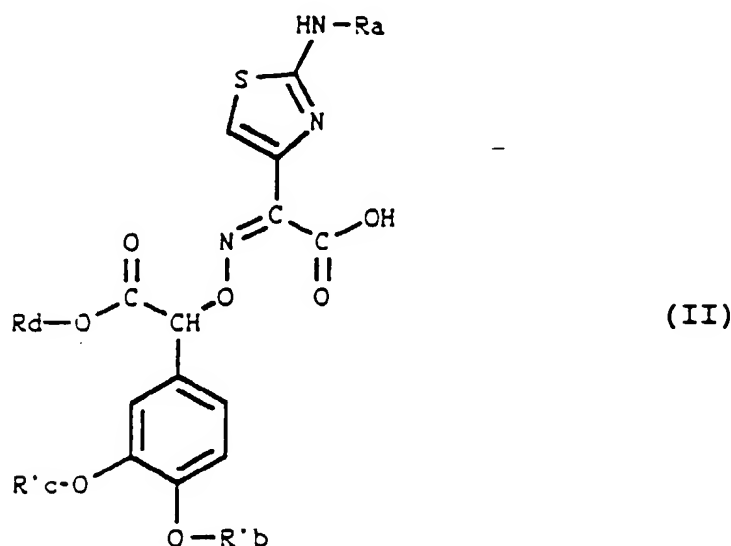


$\text{NH}-\text{CO}-\text{Q}$ ,  $\text{CN}$ ,  $\text{CH}_2-\text{CN}$  und  $\text{CH}_2-\text{SQ}$  bedeuten, wobei Q und Q' gleich oder verschieden sind und ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeuten, P, P' und P'' gleich oder verschieden sind und einen Alkylrest mit höchstens 4 Kohlenstoffatomen bedeuten, der ggf. durch einen der vorstehend für R und R' angegebenen Substituenten substituiert ist, wobei das Symbol angibt, daß P und P' ggf. mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocyclus mit 5 oder 6 Kettengliedern bilden können,

$R_b$  und  $R_c$  gleich oder verschieden sind und ein Wasserstoffatom oder eine Acylgruppe bedeuten, die unter Acetyl-, Propionyl- und Benzoylresten ausgewählt ist,

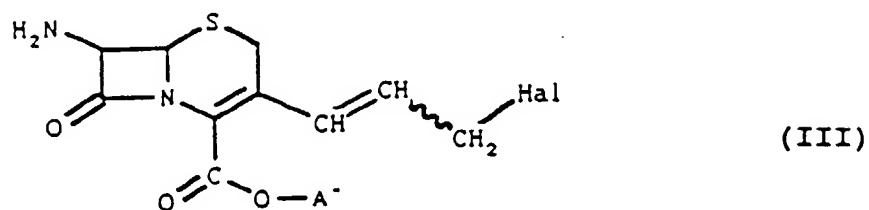
A und A' gleich oder verschieden sind und ein Wasserstoffatom, ein Äquivalent eines Alkalimetalls, Erdalkalimetalls, von Magnesium, Ammonium oder einer organischen Aminbase bedeutet oder A und A' den Rest einer leicht spaltbaren Estergruppe bedeutet oder  $\text{CO}_2\text{A}$  die Bedeutung  $\text{CO}_2^-$  hat; wobei die Wellenlinie bedeutet, daß die Gruppe  $\text{CH}_2\text{R}_1$  sich in der E- oder Z-Stellung befinden kann,

sowie der Salze der Verbindungen der Formel (I) mit anorganischen oder organischen Säuren, dadurch gekennzeichnet, daß man eine Verbindung der Formel (II)

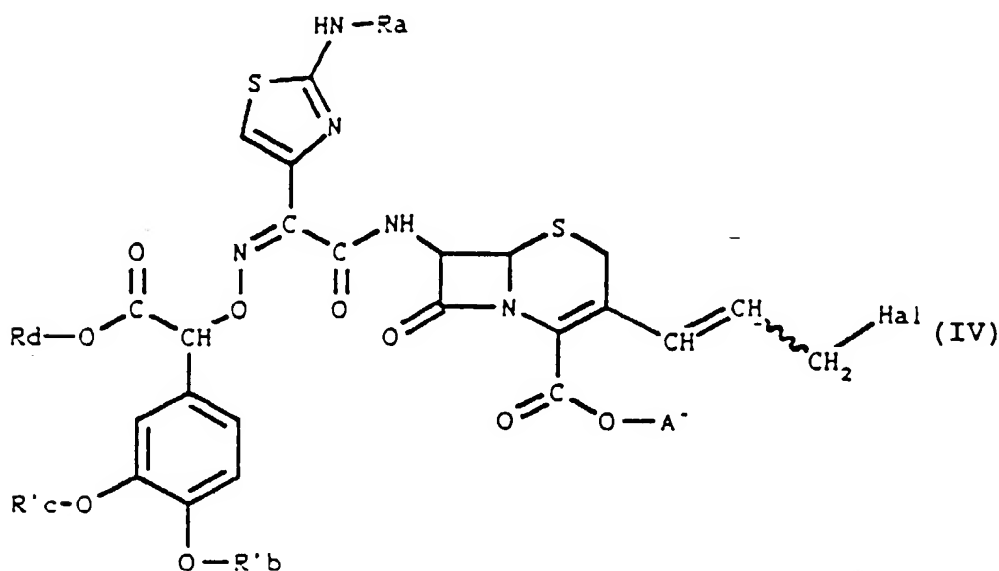


syn-Isomeres, racemisch oder optisch aktiv oder ein funktionelles Derivat der Verbindung der Formel (II), wobei  $R_a$  ein Wasserstoffatom oder eine Aminoschutzgruppe bedeutet,  $R_b$  und  $R_c$  gleich oder verschieden sind und ein Wasserstoffatom oder eine Hydroxylschutzgruppe bedeuten,  $R_d$  ein Wasserstoffatom oder den Rest einer leicht

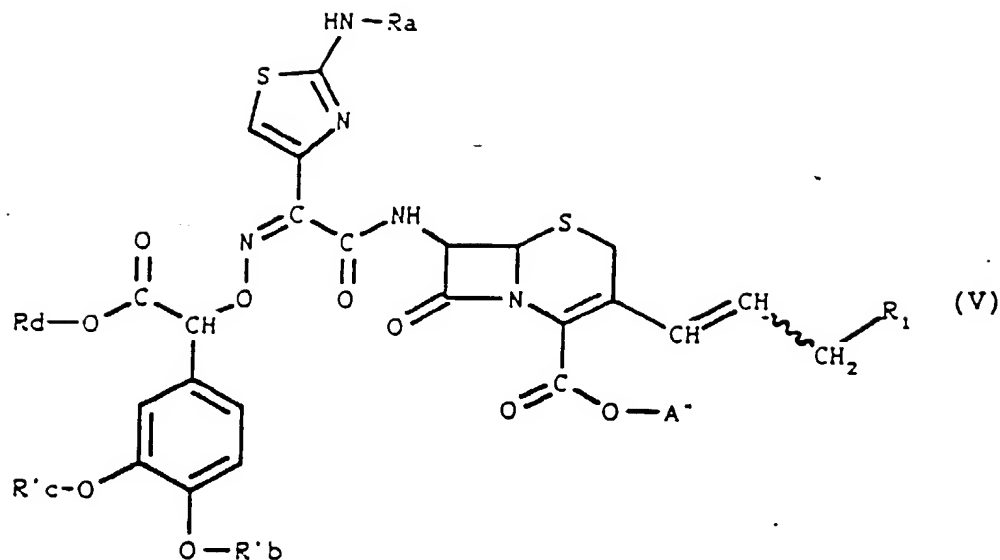
zu beseitigenden Estergruppe bedeutet, mit einer Verbindung der Formel (III) umgesetzt:



15 worin Hal ein Halogenatom bedeutet, A<sup>-</sup> ein Wasserstoffatom oder den Rest einer leicht zu beseitigenden Estergruppe bedeutet und die Wellenlinie bedeutet, daß die CH<sub>2</sub>Hal-Gruppe sich in der E- oder Z-Stellung befinden kann, wodurch man eine Verbindung der Formel (IV) erhält:



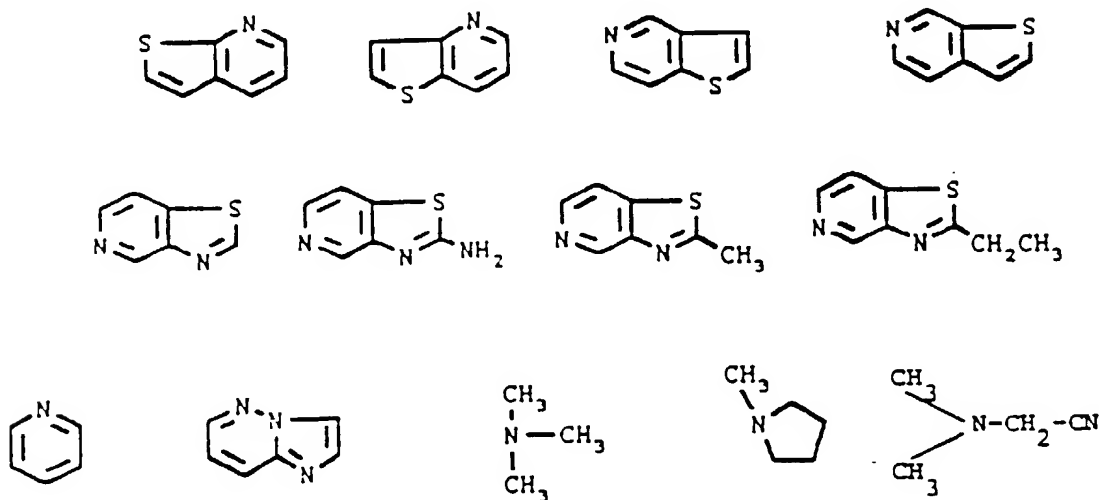
40 die man mit einem Reagenz, das zur Einführung des Restes R<sub>1</sub> befähigt ist, umsetzt, wodurch man eine Verbindung der Formel (V) erhält:



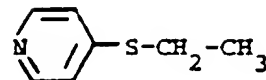
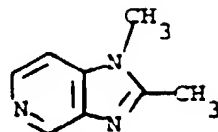
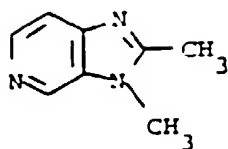
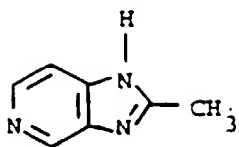
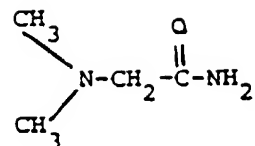
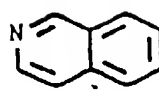
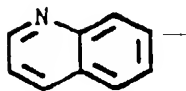
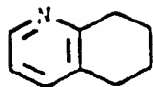
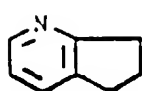
die man ggf. in ihre E- oder Z-Isomeren auftrennt, oder die Z-Isomeren in E-Isomere umwandelt, wobei man ggf. die Verbindungen der Formel (V) einer oder mehreren der folgenden Reaktionen in einer beliebigen Reihenfolge unterwirft:

- 25
- a) Abspalten der Gesamtheit oder eines Teils der Estergruppen, der Aminoschutzgruppen oder der Hydroxylschutzgruppen durch Hydrolyse oder durch Einwirkung von Thioharnstoff,
- b) Veresterung oder Salzbildung des oder der Carboxylreste mit einer Base,
- c) Salzbildung des Aminorestes mit einer Säure und
- 30 d) Auftrennung der Produkte in Form des R,S-Gemisches in die R- oder S-Form.

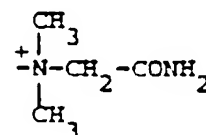
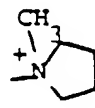
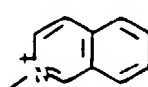
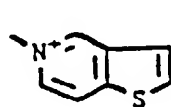
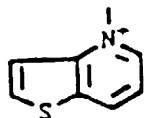
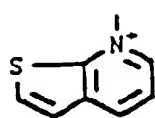
2. Herstellungsverfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Reagenz, das zur Einführung des Restes  $R_1$  befähigt ist, unter Reagenzien der folgenden Formeln ausgewählt wird:



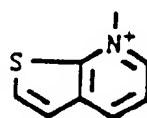




3. Herstellungsverfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Reagenz, das zur Einführung des Restes  $R_1$  befähigt ist, unter folgenden Reagenzien ausgewählt wird:



vorzugsweise:



4. Verfahren nach Anspruch 1 zur Herstellung von Verbindungen der Formel (I) gemäß der Definition in Anspruch 1, entsprechend der Formel (I'):



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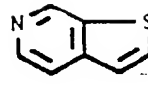
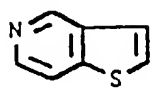
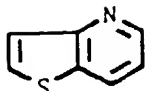
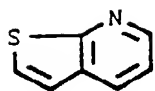
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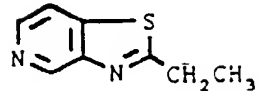
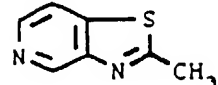
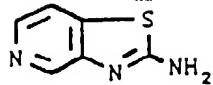
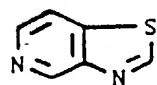
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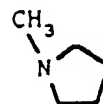
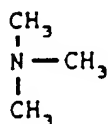
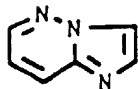
78



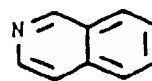
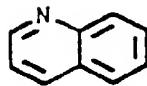
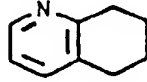
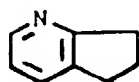
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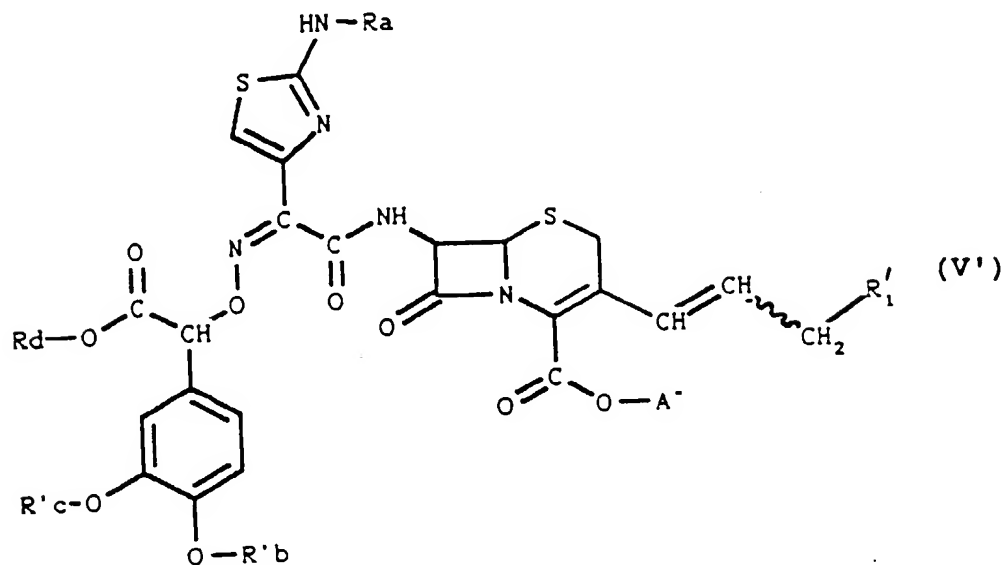


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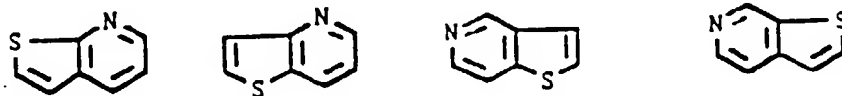
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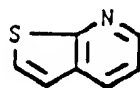
- 79

- c) Salzbildung des Aminorestes mit einer Säure und  
d) Auftrennung der Produkte in Form des R,S-Gemisches in die R- oder S-Form.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß das Reagenz, das zur Umsetzung mit der Verbindung der Formel (IV) verwendet wird, unter folgenden Reagenzien ausgewählt wird:

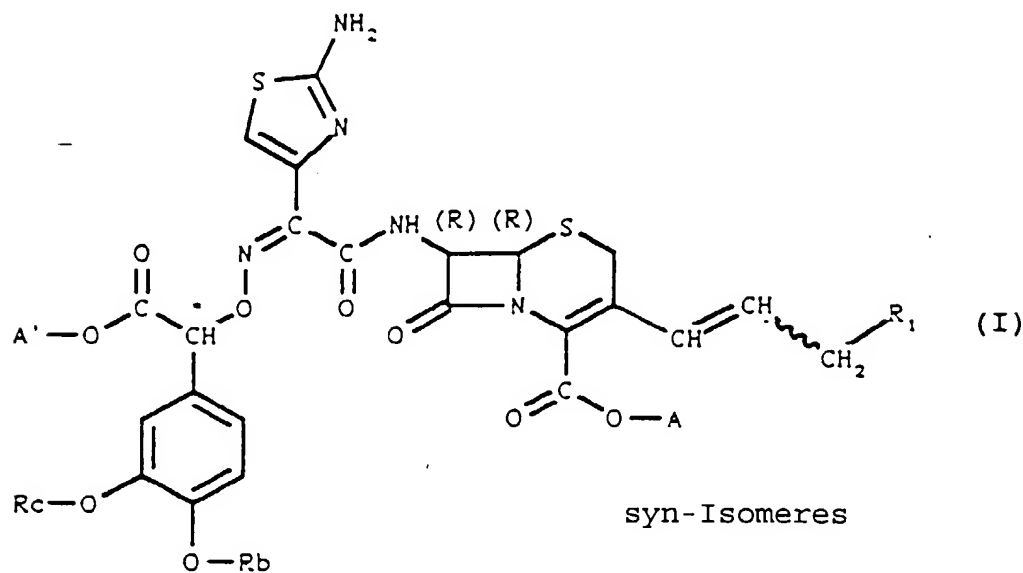


vorzugsweise:

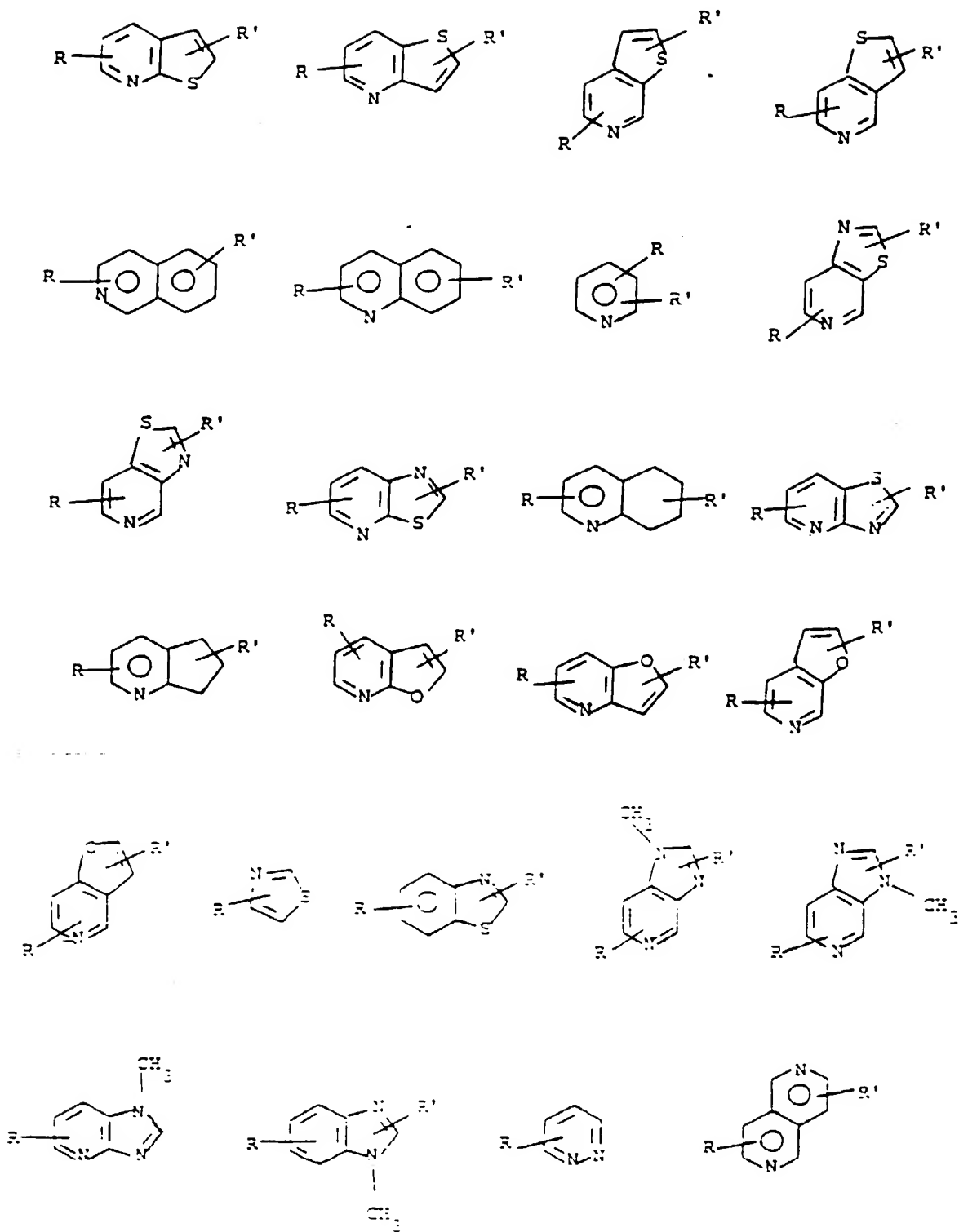


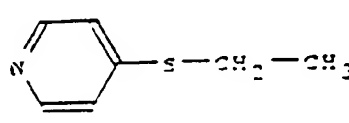
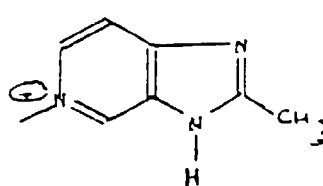
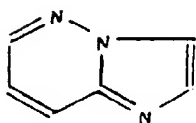
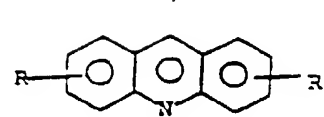
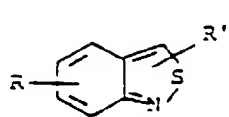
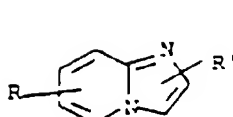
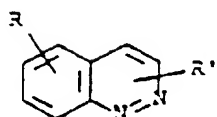
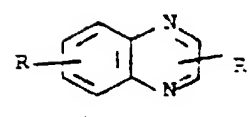
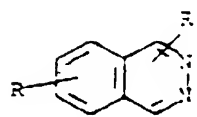
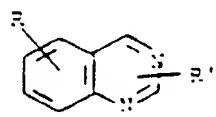
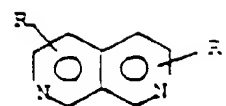
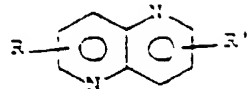
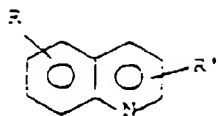
# Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung der Verbindungen der allgemeinen Formel (I) :

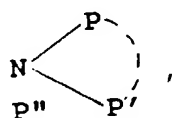


syn-Isomeres, in der R- oder S-Form oder in Form eines R,S-Gemisches, wobei in der Formel:  
R<sub>1</sub> einen unter folgenden Resten ausgewählten Rest bedeutet:



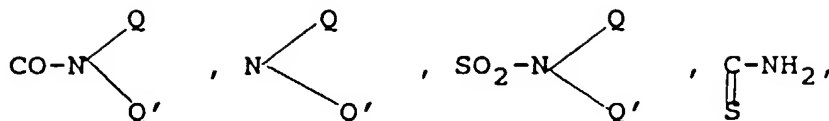


oder



in der Form von quaternärem Ammonium, wobei der Ausdruck "in der Form von quaternärem Ammonium" bedeutet, daß der Rest  $R_1$  mit der Gruppe  $-\text{CH}=\text{CH}-\text{CH}_2-$  über das Stickstoffatom oder über eines der Stickstoffatome, die er aufweist, gebunden ist,

worin R und R' gleich oder verschieden sind und ein Wasserstoffatom, einen Alkylrest mit 1 bis 4 Kohlenstoffatomen, einen Alkoxyrest mit 1 bis 4 Kohlenstoffatomen, ein Halogenatom, einen Rest der Formeln  $\text{CO}_2-\text{Q}$ ,

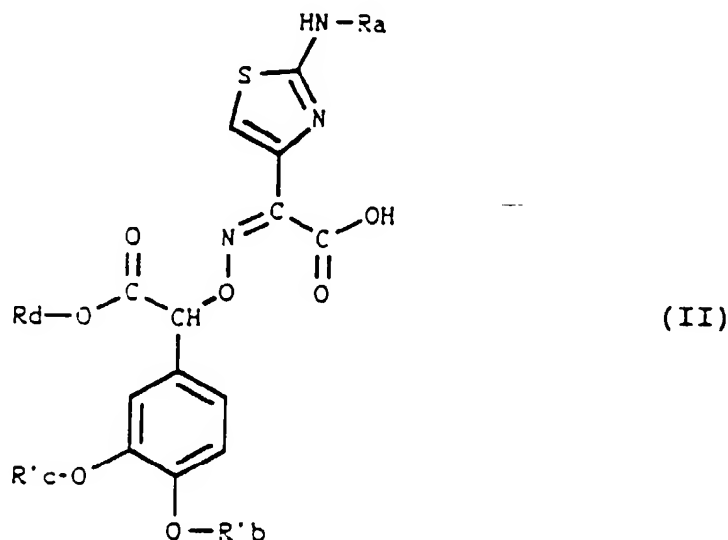


NH-CO-Q, CN, CH<sub>2</sub>-CN und CH<sub>2</sub>-SQ bedeuten, wobei Q und Q' gleich oder verschieden sind und ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeuten, P, P' und P'' gleich oder verschieden sind und einen Alkylrest mit höchstens 4 Kohlenstoffatomen bedeuten, der ggf. durch einen der vorstehend für R und R' angegebenen Substituenten substituiert ist, wobei das Symbol } angibt, daß P und P' ggf. mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocyclus mit 5 oder 6 Kettengliedern bilden können,

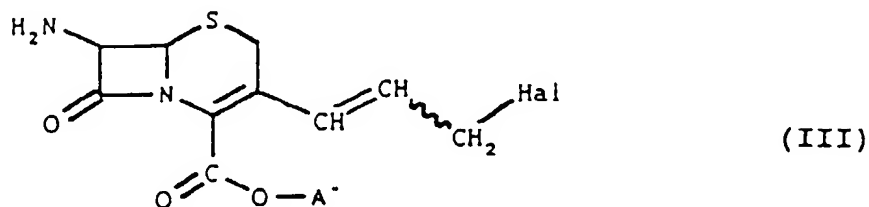
R<sub>b</sub> und R<sub>c</sub> gleich oder verschieden sind und ein Wasserstoffatom oder eine Acylgruppe bedeuten, die unter Acetyl-, Propionyl- und Benzoylresten ausgewählt ist,

A und A' gleich oder verschieden sind und ein Wasserstoffatom, ein Äquivalent eines Alkalimetalls, Erdalkalimetalls, von Magnesium, Ammonium oder einer organischen Aminbase bedeutet oder A und A' den Rest einer leicht spaltbaren Estergruppe bedeutet oder CO<sub>2</sub>A die Bedeutung CO<sub>2</sub><sup>-</sup> hat; wobei die Wellenlinie bedeutet, daß die Gruppe CH<sub>2</sub>R<sub>1</sub> sich in der E- oder Z-Stellung befinden kann,

sowie der Salze der Verbindungen der Formel (I) mit anorganischen oder organischen Säuren, dadurch gekennzeichnet, daß man eine Verbindung der Formel (II)

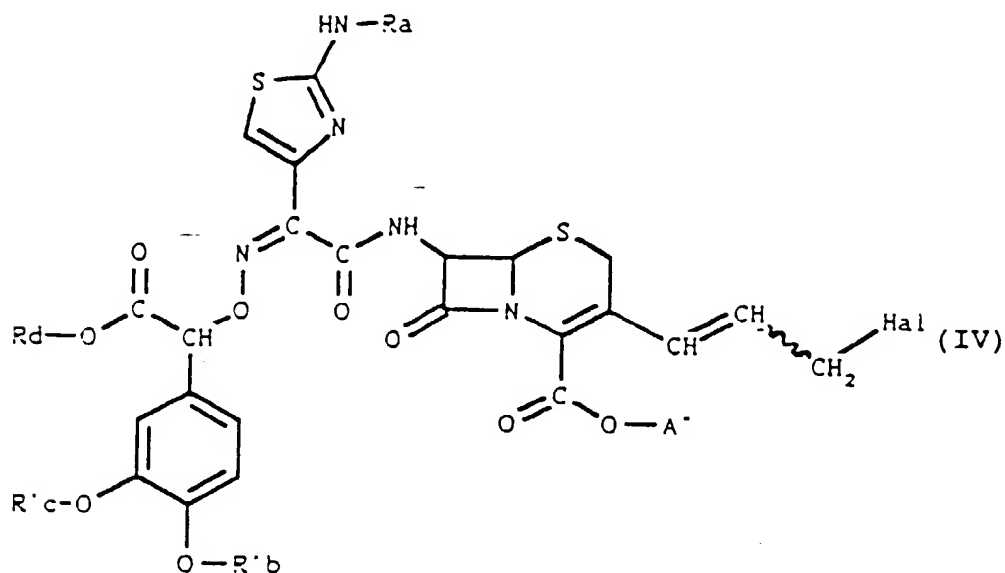


syn-Isomeres, racemisch oder optisch aktiv oder ein funktionelles Derivat der Verbindung der Formel (II), wobei R<sub>a</sub> ein Wasserstoffatom oder eine Aminoschutzgruppe bedeutet, R<sub>b</sub> und R<sub>c</sub> gleich oder verschieden sind und ein Wasserstoffatom oder eine Hydroxylschutzgruppe bedeuten, R<sub>d</sub> ein Wasserstoffatom oder den Rest einer leicht zu beseitigenden Estergruppe bedeutet, mit einer Verbindung der Formel (III) umgesetzt:

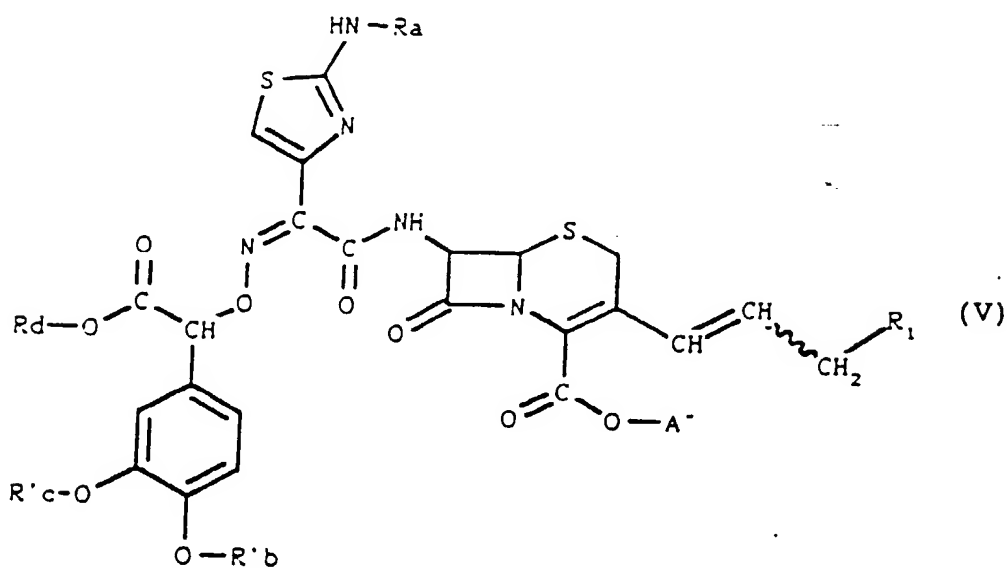


worin Hal ein Halogenatom bedeutet, A<sup>+</sup> ein Wasserstoffatom oder den Rest einer leicht zu beseitigenden

Estergruppe bedeutet und die Wellenlinie bedeutet, daß die  $\text{CH}_2\text{Hal}$ -Gruppe sich in der E- oder Z-Stellung befinden kann, wodurch man eine Verbindung der Formel (IV) erhält:



die man mit einem Reagenz, das zur Einführung des Restes  $\text{R}_1$  befähigt ist, umsetzt, wodurch man eine Verbindung der Formel (V) erhält:



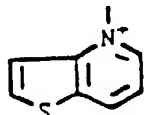
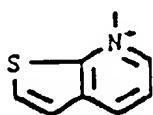
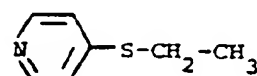
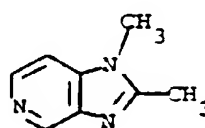
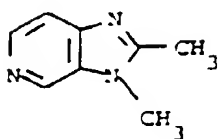
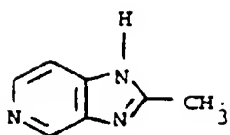
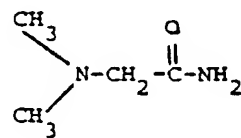
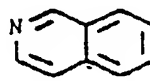
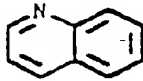
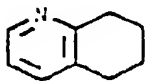
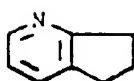
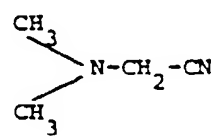
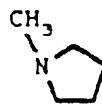
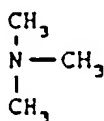
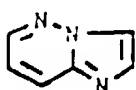
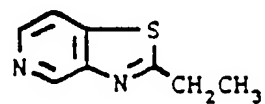
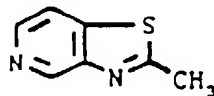
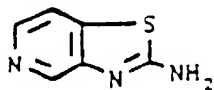
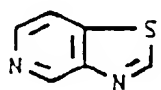
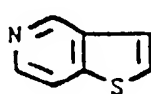
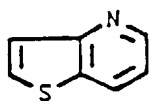
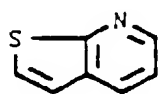
die man ggf. in ihre E- oder Z-Isomeren auftrennt, oder die Z-Isomeren in E-Isomere umwandelt, wobei man ggf. die Verbindungen der Formel (V) einer oder mehreren der folgenden Reaktionen in einer beliebigen Reihenfolge unterwirft:

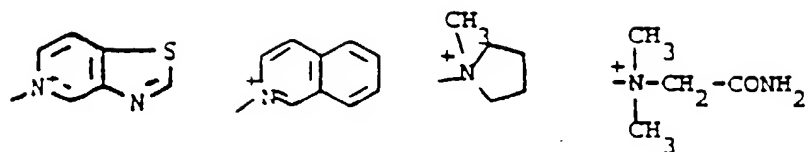
- Abspalten der Gesamtheit oder eines Teils der Estergruppen, der Aminoschutzgruppen oder der Hydroxylschutzgruppen durch Hydrolyse oder durch Einwirkung von Thioharnstoff,
- Veresterung oder Salzbildung des oder der Carboxylreste mit einer Base,
- Salzbildung des Aminorestes mit einer Säure und



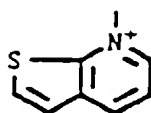
d) Auftrennung der Produkte in Form des R,S-Gemisches in die R- oder S-Form.

2. Herstellungsverfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Reagenz, das zur Einführung des Restes  $R_1$  befähigt ist, unter Reagenzien der folgenden Formeln ausgewählt wird:

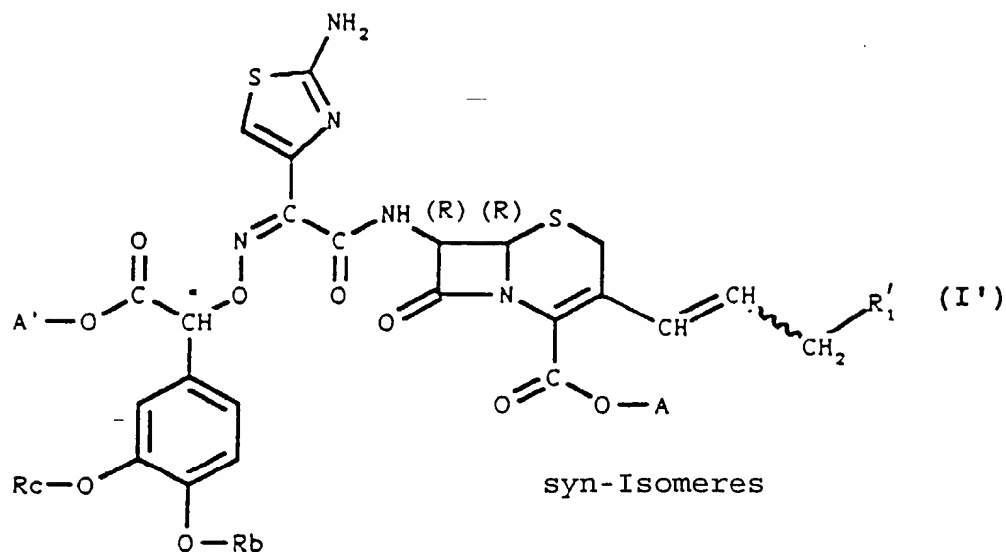




vorzugsweise

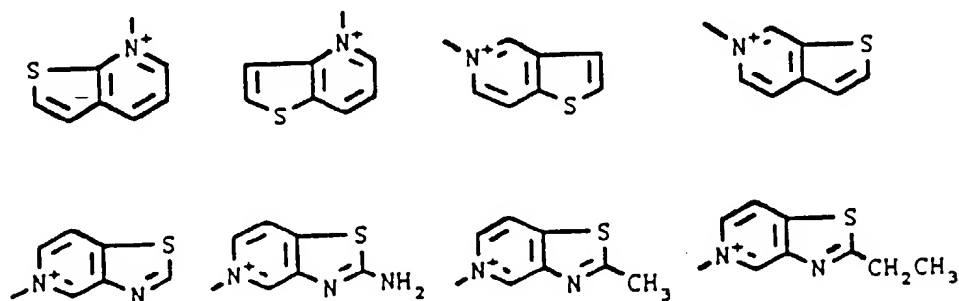


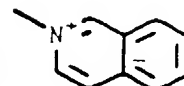
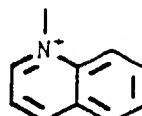
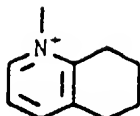
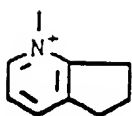
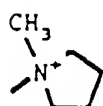
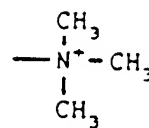
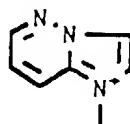
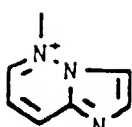
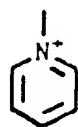
4. Verfahren nach Anspruch 1 zur Herstellung von Verbindungen der Formel (I) gemäß der Definition in Anspruch 1, entsprechend der Formel (I'):



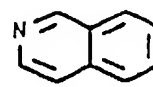
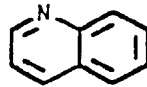
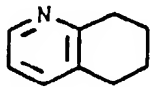
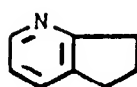
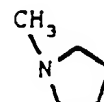
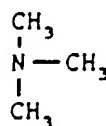
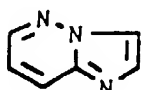
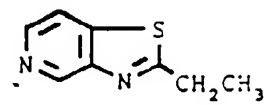
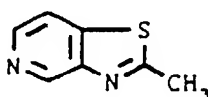
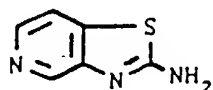
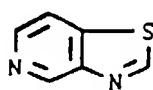
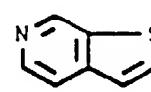
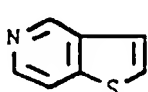
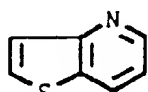
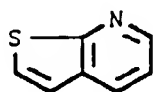
syn-Isomeres, in der R- oder S-Form oder in Form eines R,S-Gemisches, wobei in der Formel:

A, A', R<sub>b</sub> und R<sub>c</sub> eine unveränderte Bedeutung haben und R'<sub>1</sub> einen Rest bedeutet, der unter folgenden Resten ausgewählt ist:

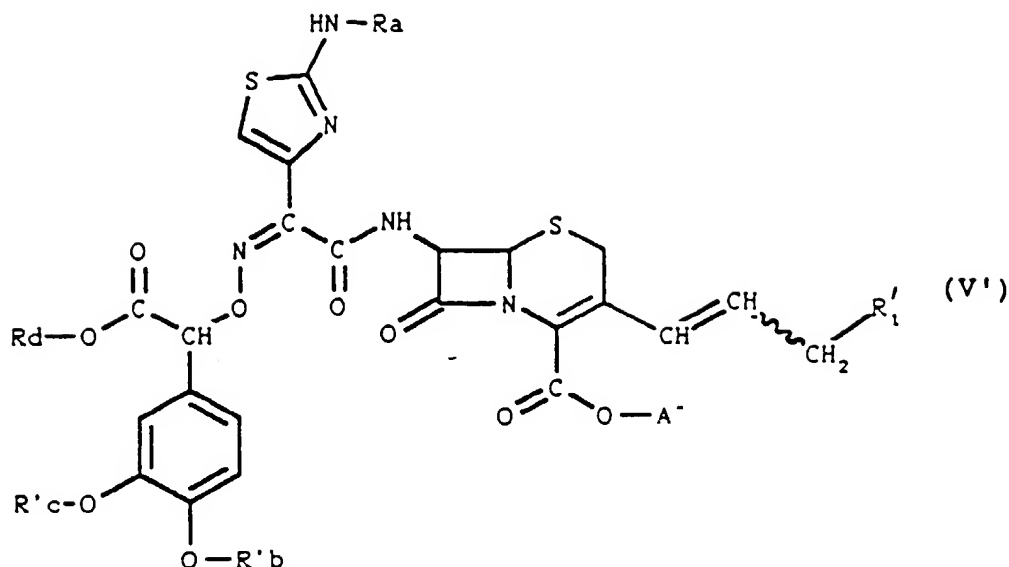




sowie von Salzen der Verbindungen der Formel (I') mit anorganischen oder organischen Säuren, dadurch gekennzeichnet, daß man eine Verbindung der Formel (II) mit einer Verbindung der Formel (III), die der Definition in Anspruch 1 entsprechen, umsetzt, anschließend die erhaltene Verbindung der Formel (IV) mit einem Reagenz, das unter folgenden Reagenzien ausgewählt wird, umsetzt:



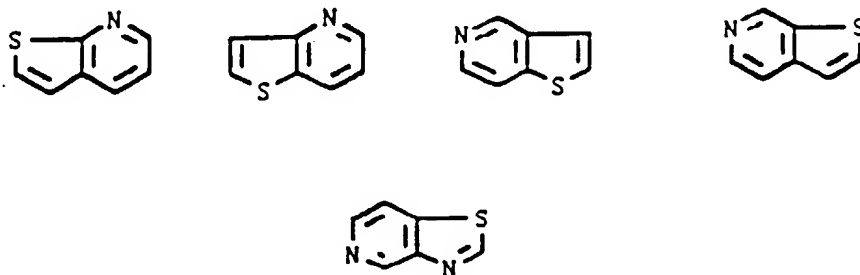
wodurch man eine Verbindung der Formel (V') erhält:



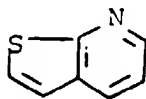
25 die man ggf. in ihre E- oder Z-Isomeren auftrennt, oder die Z-Isomeren in E-Isomere umwandelt, wobei man ggf. die Verbindungen der Formel (V) einer oder mehreren der folgenden Reaktionen in einer beliebigen Reihenfolge unterwirft:

- 30 a) Abspalten der Gesamtheit oder eines Teils der Estergruppen, der Aminoschutzgruppen oder der Hydroxylschutzgruppen durch Hydrolyse oder durch Einwirkung von Thioharnstoff,  
 b) Veresterung oder Salzbildung des oder der Carboxylreste mit einer Base,  
 c) Salzbildung des Aminorestes mit einer Säure und  
 d) Auftrennung der Produkte in Form des R,S-Gemisches in die R- oder S-Form.

- 35 5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß das Reagenz, das zur Umsetzung mit der Verbindung der Formel (IV) verwendet wird, unter folgenden Reagenzien ausgewählt wird:



50 vorzugsweise:



6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die verwendeten Ausgangsverbindungen und Reagenzien so auswählt, daß man eine der folgenden Verbindungen herstellt:

- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-5-[3-[7-[[2-Amino-4-thiazolyl][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thiazolo[4,5-c]pyridinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon,
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-7-[3-[7-[[2-Amino-4-thiazolyl][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-thieno[2,3-b]pyridinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon und insbesondere in der S-Form,
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-2-[3-[7-[[2-Amino-4-thiazolyl][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-isochinolinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon,
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-1-[3-[7-[[2-Amino-4-thiazolyl][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-1-methylpyrrolidinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon,
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-1-(3-[7-[[2-Amino-4-thiazolyl][1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon und
- [6R-[3(E),6 $\alpha$ ,7 $\beta$ (Z)]]-N-(2-Amino-2-oxoethyl)-3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in der R- oder S-Form oder in Form eines R,S-Gemisches und in Form eines internen Salzes oder eines Salzes mit Alkalimetallen, Erdalkalimetallen, Magnesium, Ammoniak, organischen Aminbasen, Säuren und leicht spaltbaren Estern davon.

7. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen, dadurch gekennzeichnet, daß man als Wirkstoff mindestens eines der Derivate der Formel (I) gemäß der Definition in Anspruch 1 sowie deren pharmazeutisch verträgliche Salze mit Säuren in einer für diese Verwendung bestimmten Form bereitstellt.

8. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen, dadurch gekennzeichnet, daß man als Wirkstoff mindestens eines der Derivate der Formel (I') gemäß der Definition in Anspruch 4 sowie deren pharmazeutisch verträgliche Salze mit Säuren in einer für diese Verwendung bestimmten Form bereitstellt.

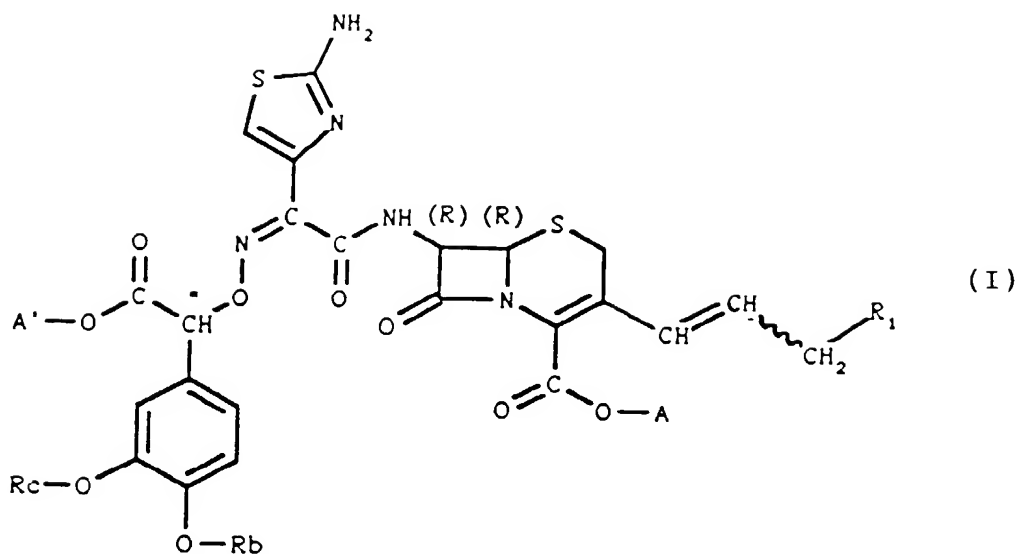
9. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen, dadurch gekennzeichnet, daß man als Wirkstoff mindestens eines der Derivate der Formel (I) gemäß der Definition in Anspruch 6 sowie deren pharmazeutisch verträgliche Salze mit Säuren in einer für diese Verwendung bestimmten Form bereitstellt.

10. Verbindungen der Formel (IV) und Verbindungen der Formel (V), worin R<sub>a</sub> eine Aminoschutzgruppe bedeutet, wobei die Formeln (IV) und (V) der Definition in Anspruch 5 entsprechen, als gewerblich einzusetzende Verbindungen.

## Claims

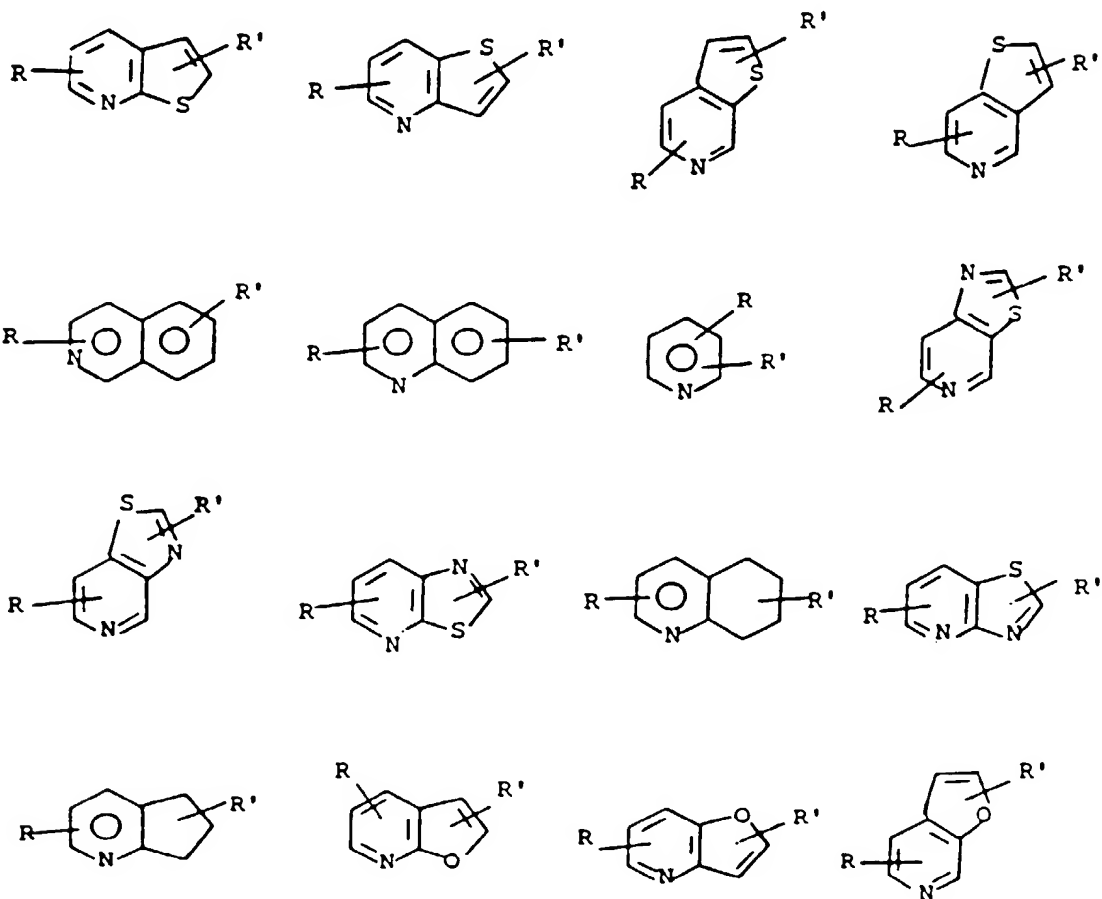
Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

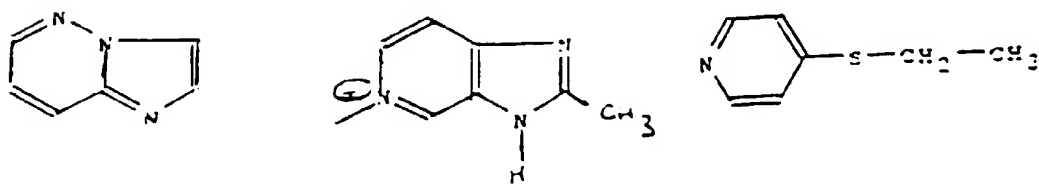
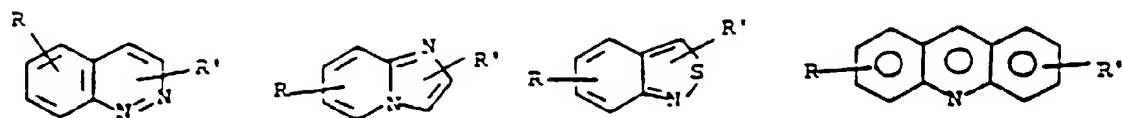
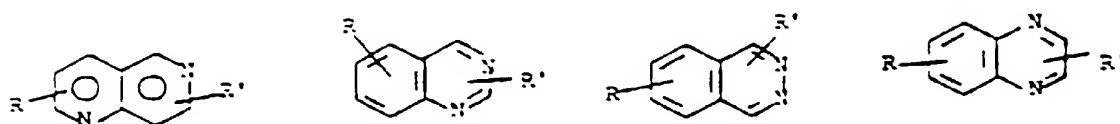
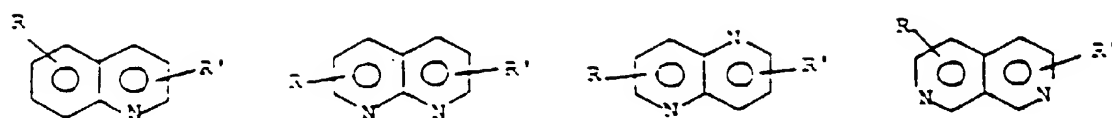
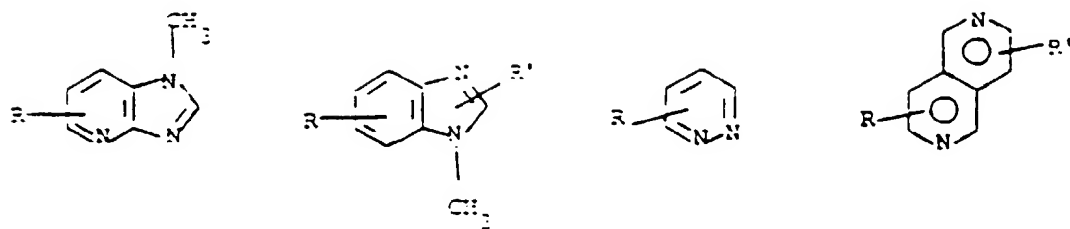
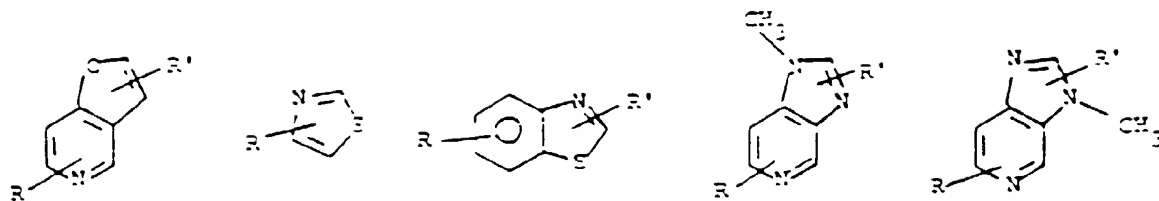
1. The products of general formula (I):



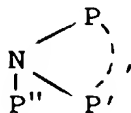
SYN isomer

25 syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:  
 $R_1$  represents a radical chosen from the following radicals:

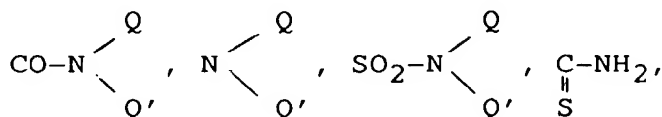




or



in the quaternary ammonium form, the expression in quaternary ammonium form indicating that the  $R_1$  radical is linked to the  $-\text{CH}=\text{CH}=\text{CH}_2$  group by the nitrogen atom or atoms which it contains, in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals:  $\text{CO}_2\text{-Q}$ ,

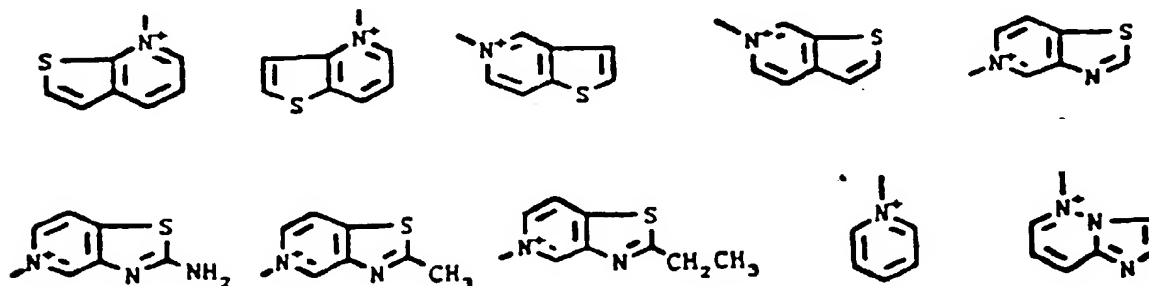


$\text{NH-CO-Q}$ ,  $\text{CN}$ ,  $\text{CH}_2\text{-CN}$ ,  $\text{CH}_2\text{-SQ}$  in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol } indicating that P and P'' can optionally form, with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 members.

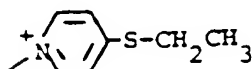
$R_b$  and  $R_c$ , identical or different, represent a hydrogen atom or an acyl group, chosen from the acetyl, propionyl and benzoyl radicals,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or  $\text{CO}_2\text{A}$  represents  $\text{CO}_2^-$ ; the wavy line means that the  $\text{CH}_2\text{R}_1$  group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

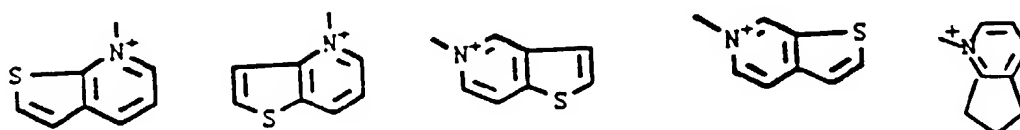
2. The products of general formula (I) as defined in claim 1 in which  $R_1$  is chosen from the following radicals:



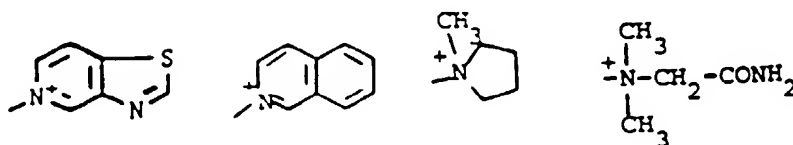




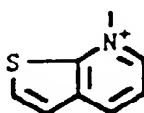
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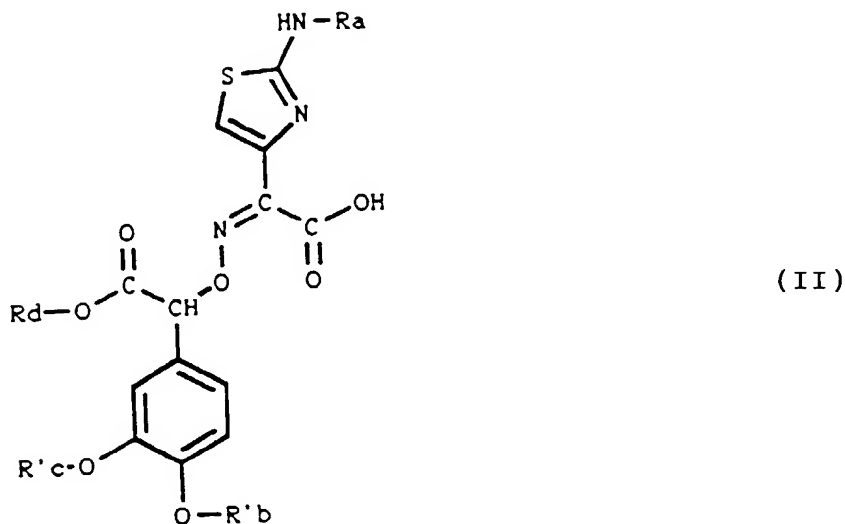


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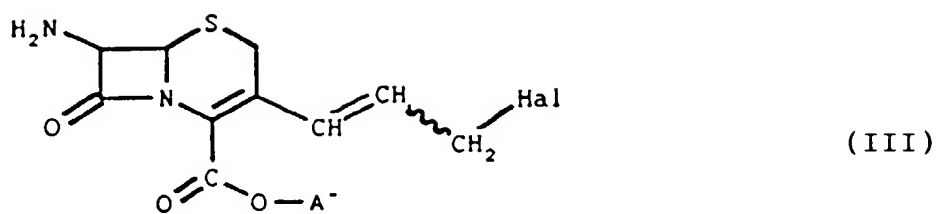
metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z))]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in the R or S form or the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E), 6alpha, 7beta(Z))]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E), 6alpha, 7beta(Z))]-N-(2-amino-2-oxoethyl)-3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters.

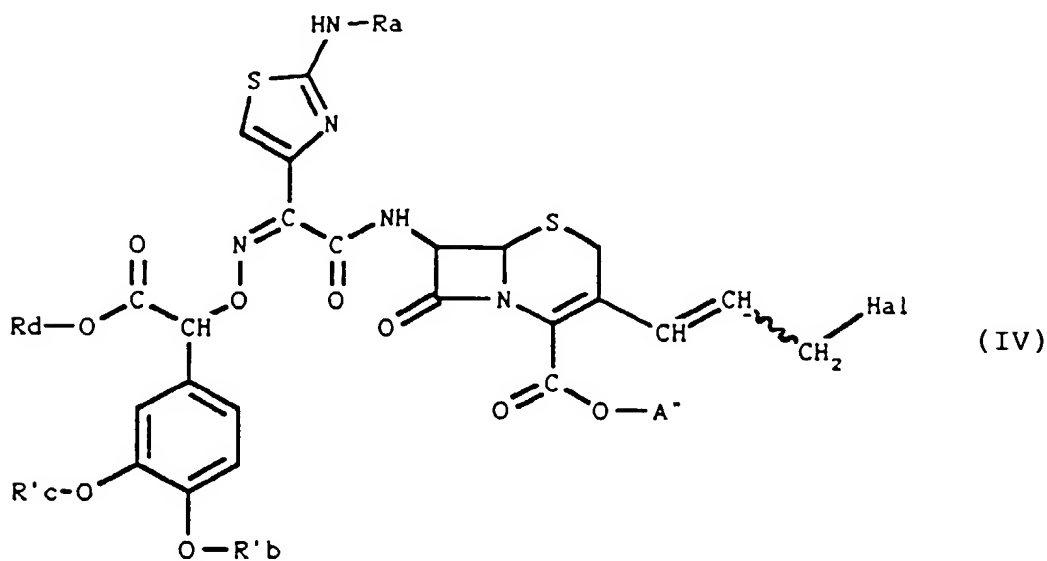
6. Preparation process for the products of formula (I) as defined in claim 1, characterized in that a product of formula (II):



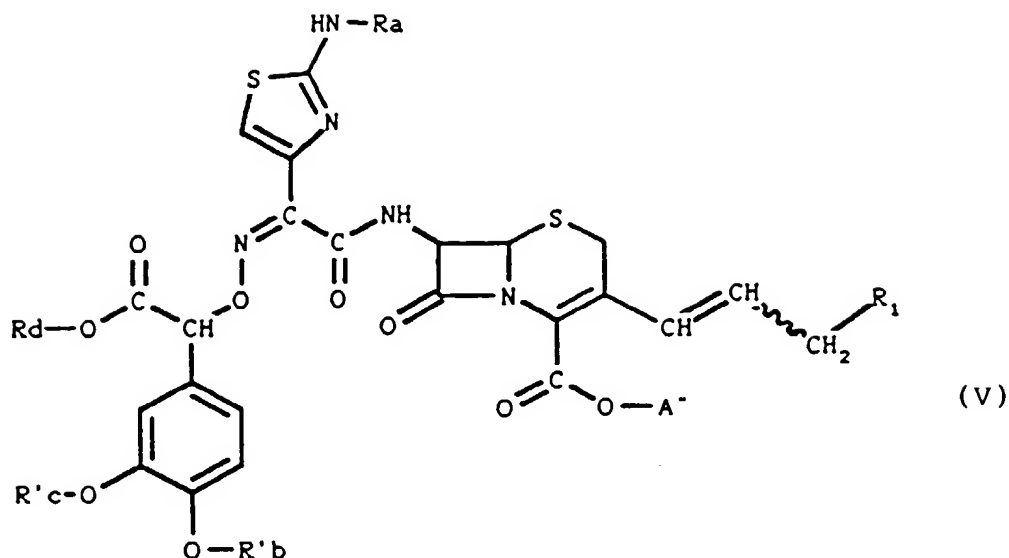
racemic or optically active syn isomer or a functional derivative of the product of formula (II), in which  $R_a$  represents a hydrogen atom or a protective group of the amino radical,  $R'_b$  and  $R'_c$ , identical or different, represent a hydrogen atom or a protective group of the hydroxyl radical,  $R_d$  represents a hydrogen atom or the remainder of an easily eliminable ester group, is reacted with a product of formula (III):



15 in which Hal represents a halogen atom, A<sup>+</sup> represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the CH<sub>2</sub>Hal group can be found in E or Z position, in order to obtain a product of formula (IV):



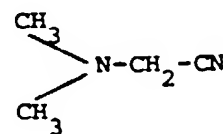
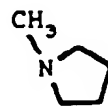
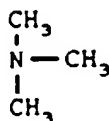
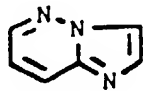
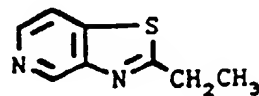
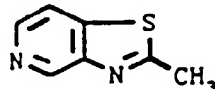
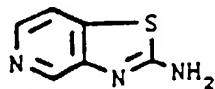
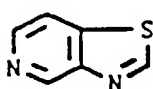
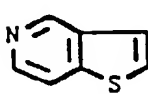
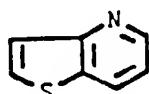
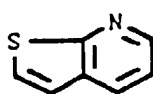
40 which is reacted with a reagent capable of introducing the R<sub>1</sub> radical in order to obtain a product of formula (V):

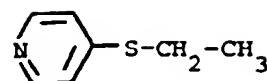
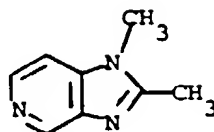
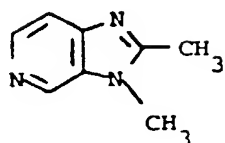
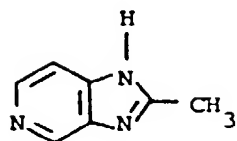
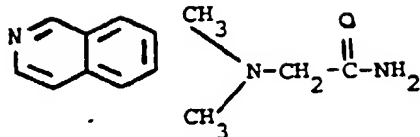
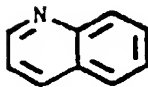
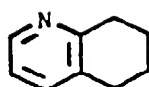
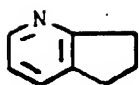


25 which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

- 30 a) cleaving, by hydrolysis or by the action of thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,  
 b) esterification or salification of the carboxylic radical or radicals by a base,  
 c) salification of the amino radical by an acid,  
 d) separation of products in the form of an R, S mixture into R or S.

- 35 7. Preparation process according to claim 6 characterized in that the reagent capable of introducing the  $R_1$  radical is chosen from the reagents of formulae:





8. As medicaments, the products corresponding to formula (I) as defined in claim 1, as well as their pharmaceutically acceptable acid salts.

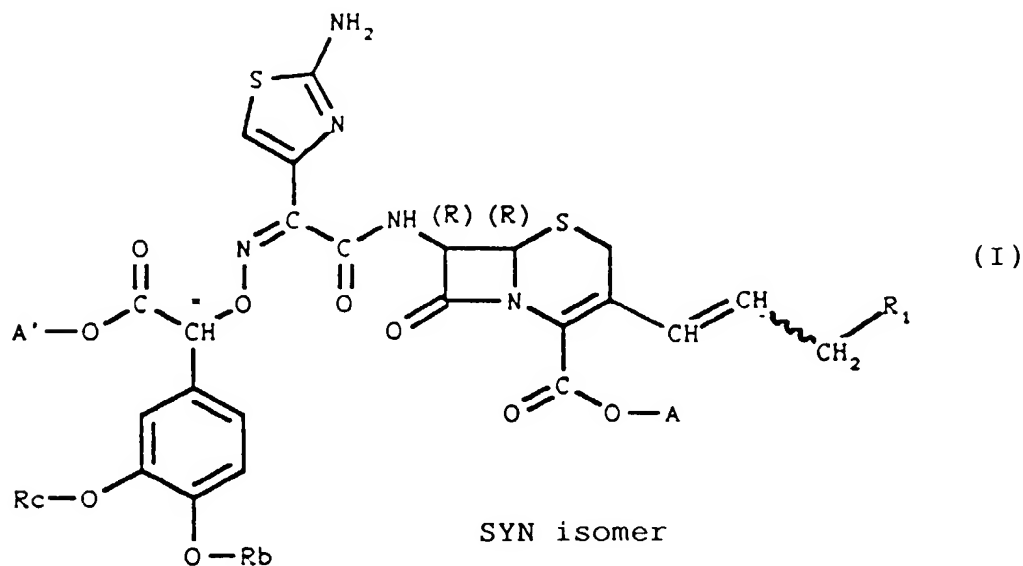
9. As medicaments, the products as defined in any one of claims 2 to 5 as well as their pharmaceutically acceptable acid salts.

10. Pharmaceutical compositions containing, as active ingredient, at least one medicament according to one of claims 8 or 9.

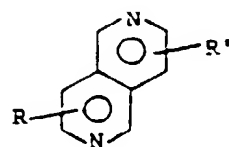
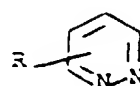
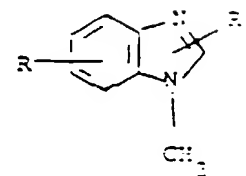
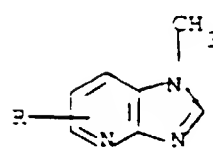
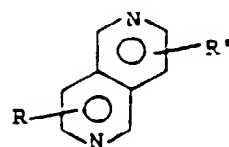
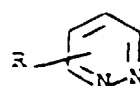
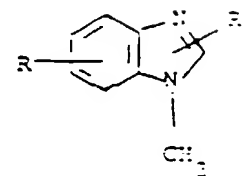
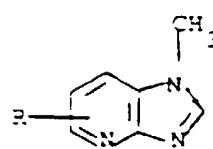
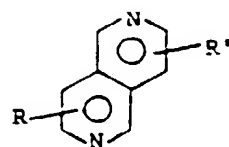
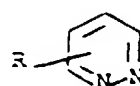
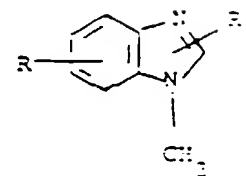
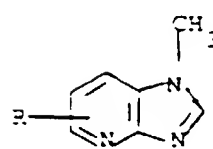
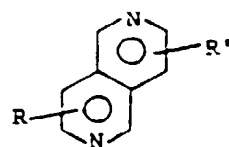
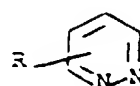
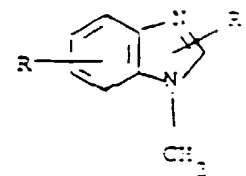
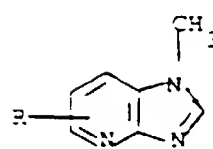
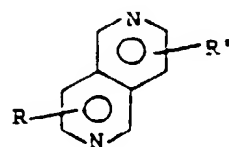
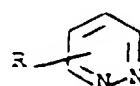
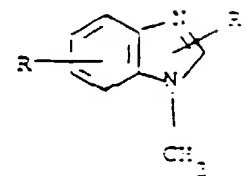
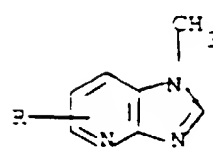
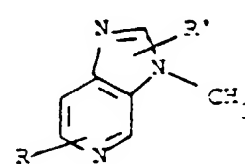
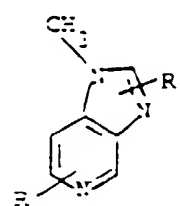
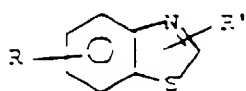
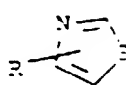
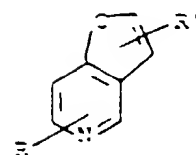
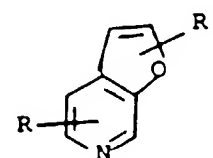
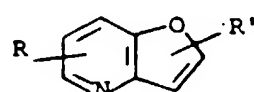
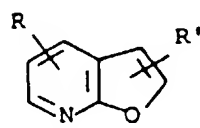
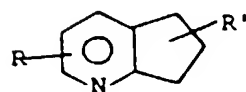
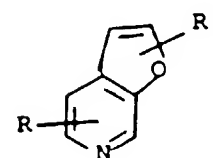
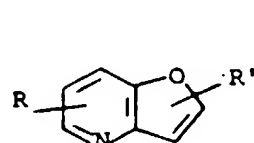
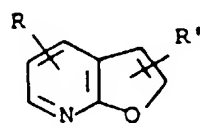
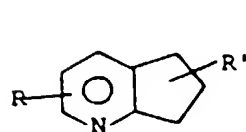
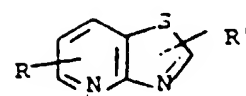
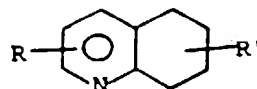
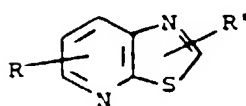
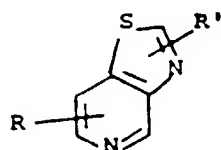
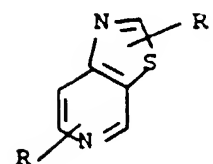
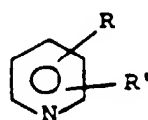
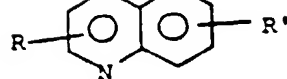
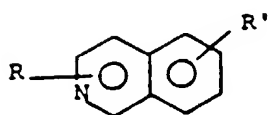
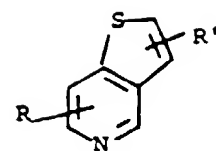
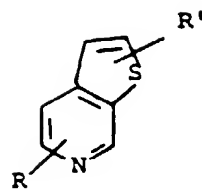
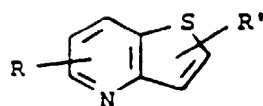
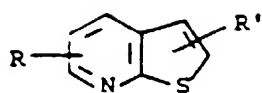
11. As industrial products, the products of formula (IV) and the products of formula (V) in which  $R_a$  represents a protective group of the amino radical, formulae (IV) and (V) being as defined in claim 6.

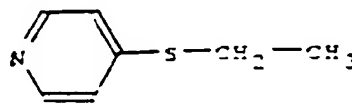
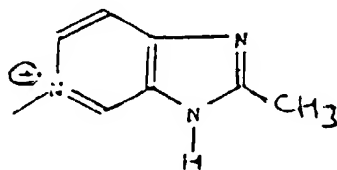
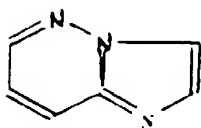
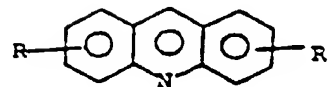
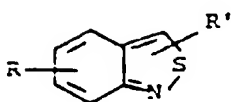
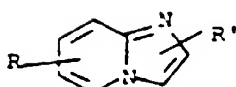
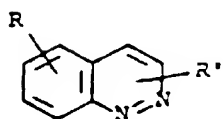
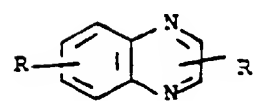
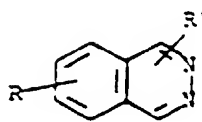
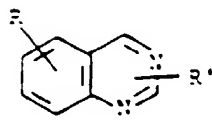
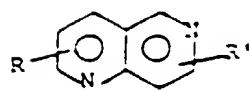
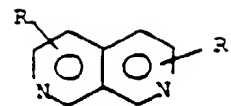
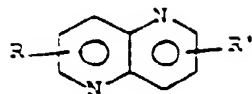
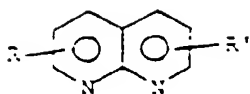
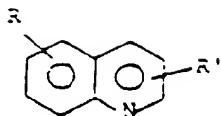
#### Claims for the following Contracting State : ES

1. Preparation process for the products of general formula (I):

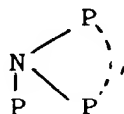


syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:  
 $R_1$  represents a radical chosen from the following radicals:

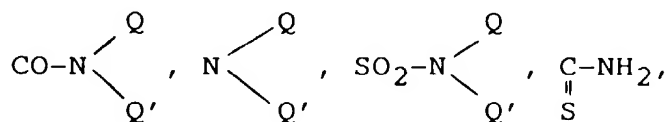




or



in the quaternary ammonium form, the expression in quaternary ammonium form indicating that the  $R_1$  radical is linked to the  $-\text{CH}=\text{CH}=\text{CH}_2$  group by the nitrogen atom or atoms which it contains, in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a  $\text{CO}_2\text{-Q}$ ,

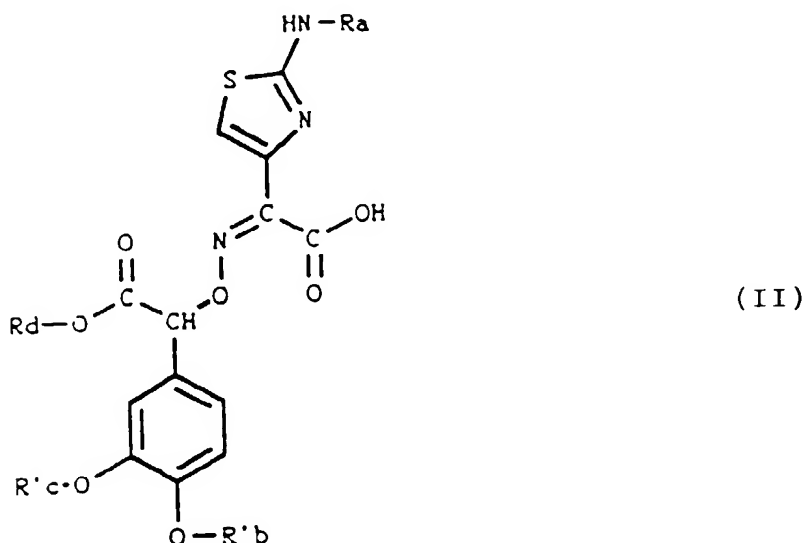


$\text{NH-CO-Q}$ ,  $\text{CN}$ ,  $\text{CH}_2\text{-CN}$ ,  $\text{CH}_2\text{-SQ}$  in which Q and Q', identical or different, represent a hydrogen atom or an alkyl

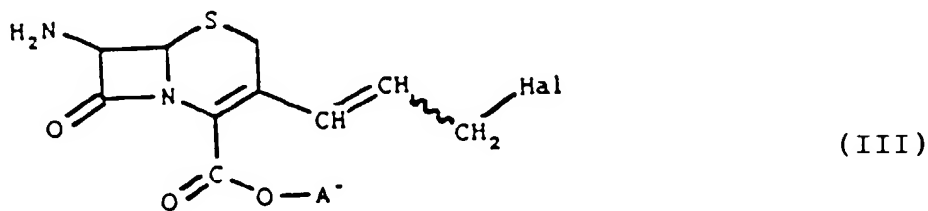
radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol  $\{$  indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 members.

R<sub>b</sub> and R<sub>c</sub>, identical or different, represent a hydrogen atom or an acyl group, chosen from the acetyl, propionyl and benzoyl radicals,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or CO<sub>2</sub>A represents CO<sub>2</sub><sup>-</sup>; the wavy line means that the CH<sub>2</sub>R<sub>1</sub> group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids, characterized in that a product of formula (II):

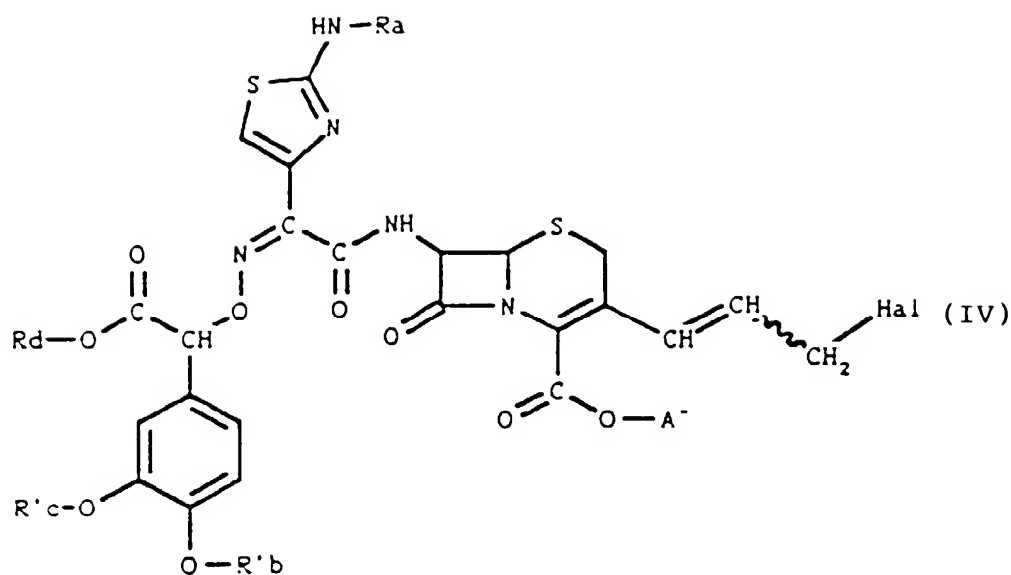


racemic or optically active syn isomer or a functional derivative of the product of formula (II), in which R<sub>a</sub> represents a hydrogen atom or a protective group of the amino radical, R<sub>b</sub> and R<sub>c</sub>, identical or different, represent a hydrogen atom or a protective group of the hydroxyl radical, R<sub>d</sub> represents a hydrogen atom or the remainder of an easily eliminable ester group, is reacted with a product of formula (III):

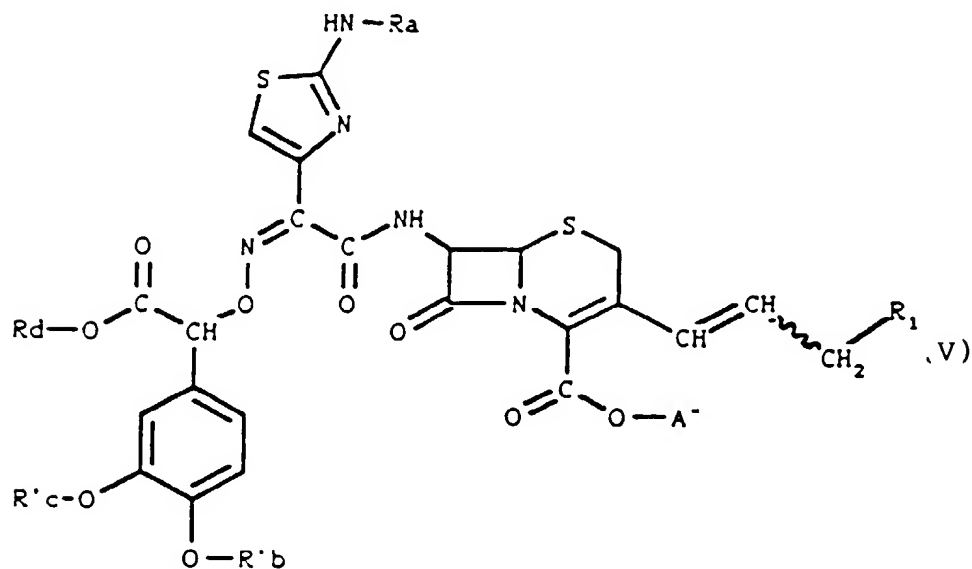


in which Hal represents a halogen atom, A' represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the CH<sub>2</sub>Hal group can be found in E or Z position, in order to obtain a product of formula (IV):





which is reacted with a reagent capable of introducing the  $\text{R}_1$  radical in order to obtain a product of formula (V):

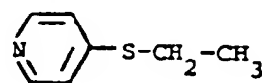
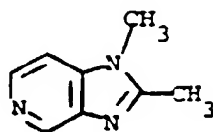
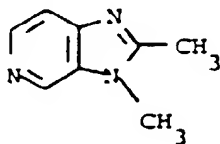
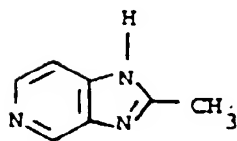
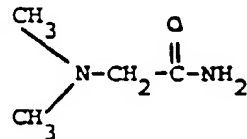
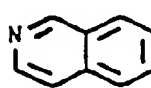
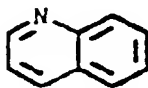
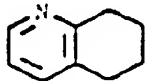
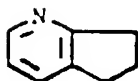
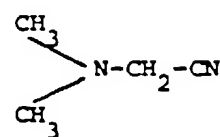
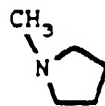
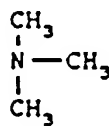
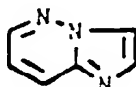
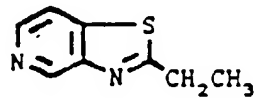
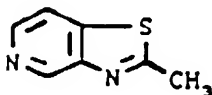
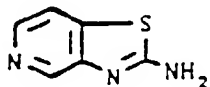
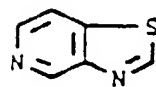
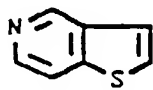
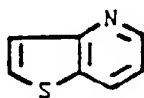
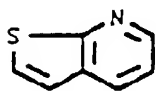


which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

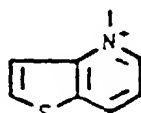
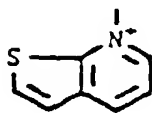
- a) cleaving, by hydrolysis or by the action of thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,
- b) esterification or salification of the carboxylic radical or radicals by a base,
- c) salification of the amino radical by an acid,

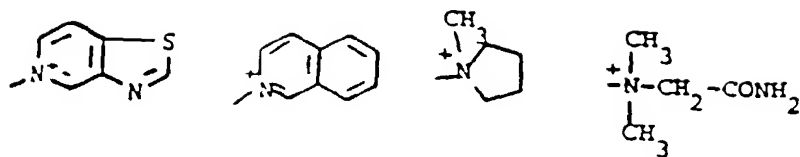
d) separation of products in the form of an R, S mixture into R or S.

2. Preparation process according to claim 1 characterized in that the reagent capable of introducing the  $R_1$  radical is chosen from the reagents of formulae:

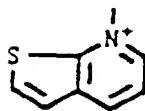


3. Preparation process according to claim 1 or 2, characterized in that the reagent capable of introducing the  $R_1$  radical is chosen from the reagents:

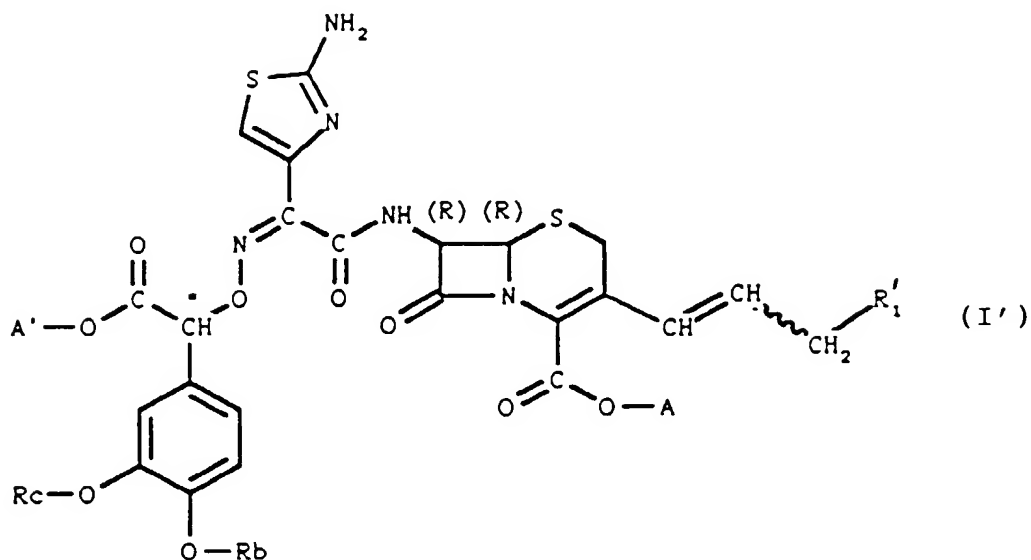




preferably:



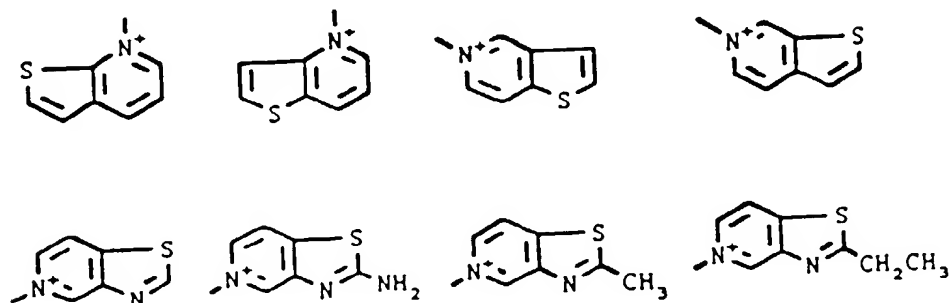
4. Process according to claim 1 for the preparation of the products of formula (I) as defined in claim 1 corresponding to formula (I'):

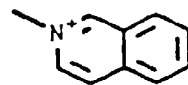
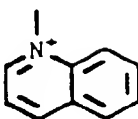
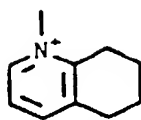
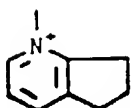
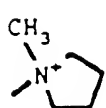
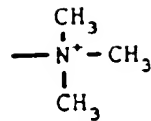
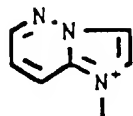
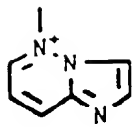
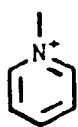


SYN isomer

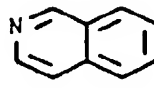
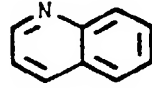
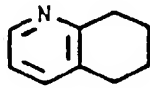
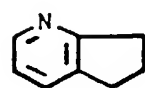
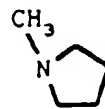
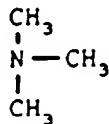
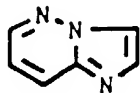
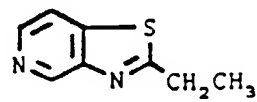
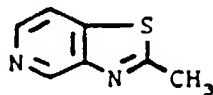
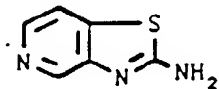
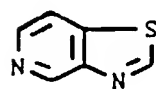
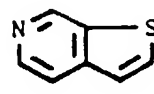
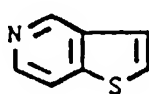
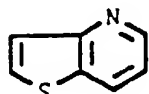
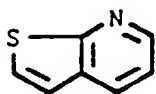
syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

A, A' R<sub>b</sub> and R<sub>c</sub> retain their previous meaning and R'<sub>1</sub> represents a radical chosen from the following radicals:

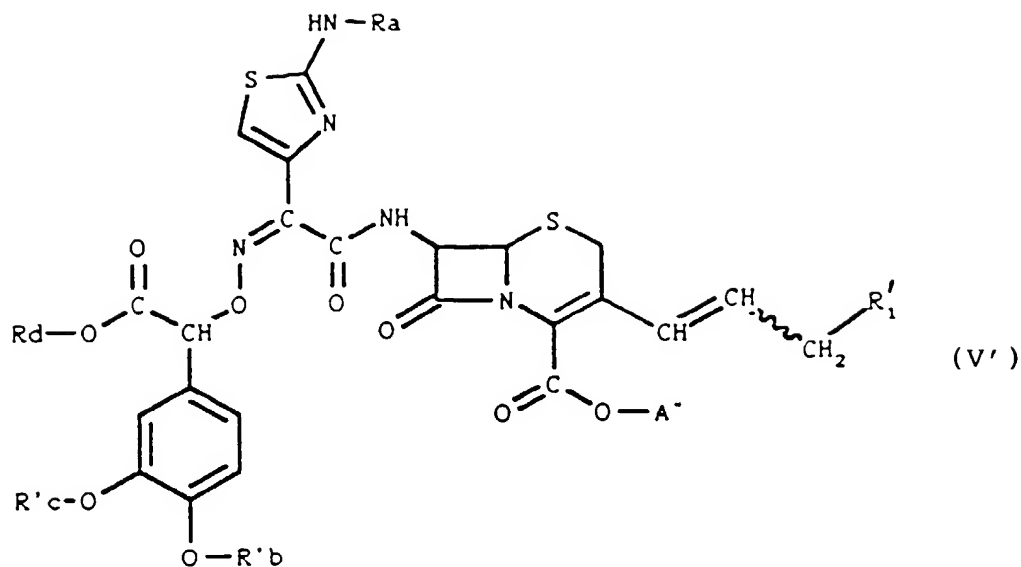




as well as the salts of the products of formula (I') with mineral or organic acids, characterized in that a product of formula (II) is reacted with a product of formula (III) defined as in claim 1, then a reagent chosen from the reagents of formula:



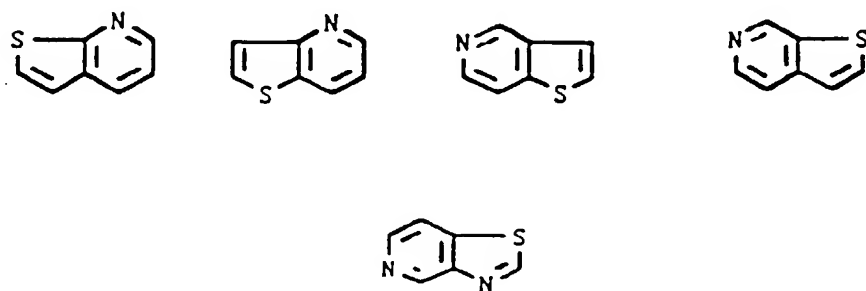
is reacted with the product of formula (IV) obtained, in order to obtain a product of formula (V'):



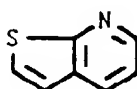
which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

- 25
- a) cleaving, by hydrolysis or by the action of the thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,
  - b) esterification or salification of the carboxylic radical or radicals by a base,
  - c) salification of the amino radical by an acid,
  - d) separation of products in the form of an R, S mixture into R or S.
- 30

5. Process according to claim 4, characterized in that the reagent used on the product of formula (IV) is chosen from the reagents:

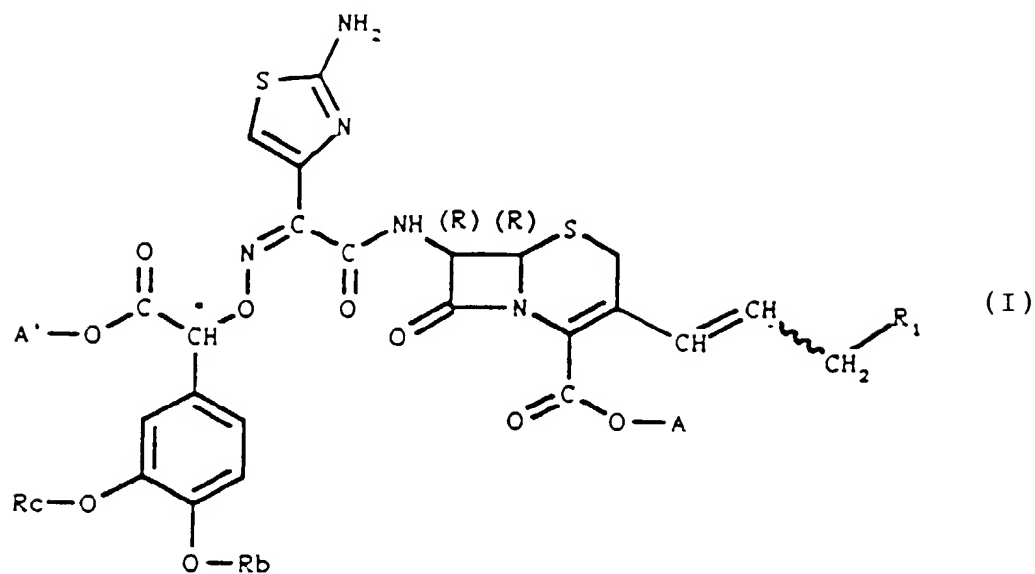


preferably:



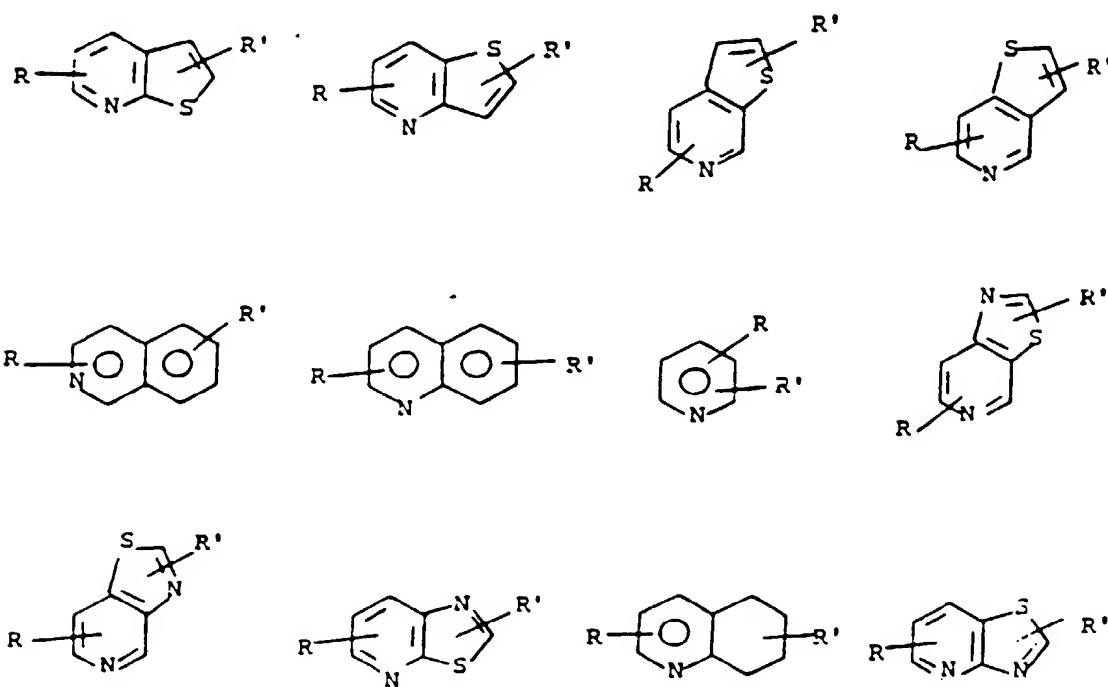
## Claims for the Contracting State: GR

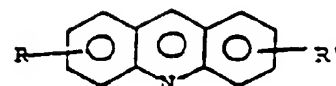
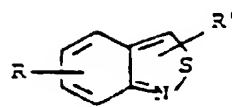
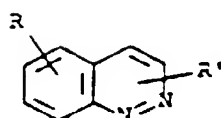
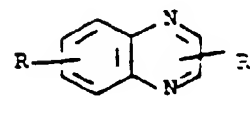
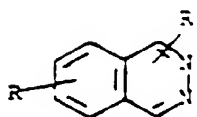
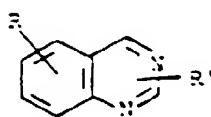
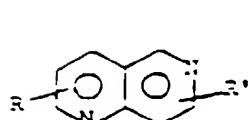
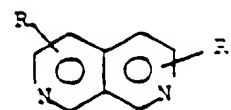
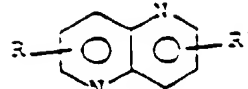
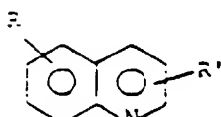
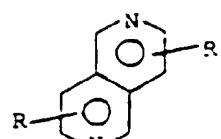
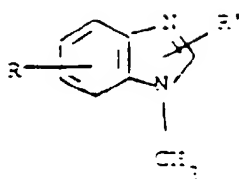
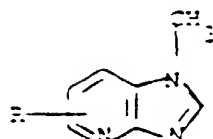
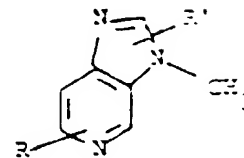
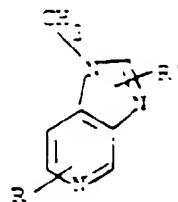
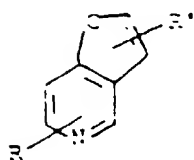
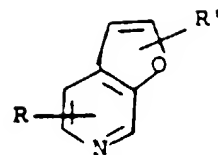
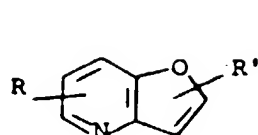
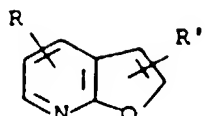
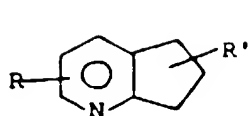
1. Preparation process for the products of general formula (I):

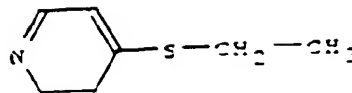
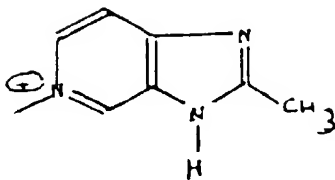
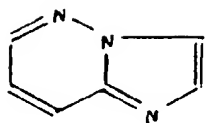


SYN isomer

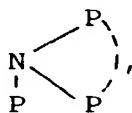
syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:  
 $\text{R}_1$  represents a radical chosen from the following radicals:



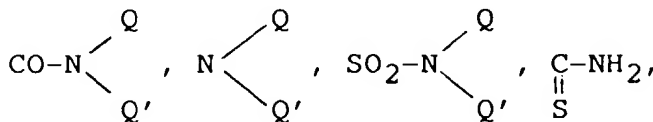




or



in the quaternary ammonium form, the expression in quaternary ammonium form indicating that the  $R_1$  radical is linked to the  $-\text{CH}=\text{CH}=\text{CH}_2$  group by the nitrogen atom or atoms which it contains, in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a  $\text{CO}_2\text{-Q}$ ,

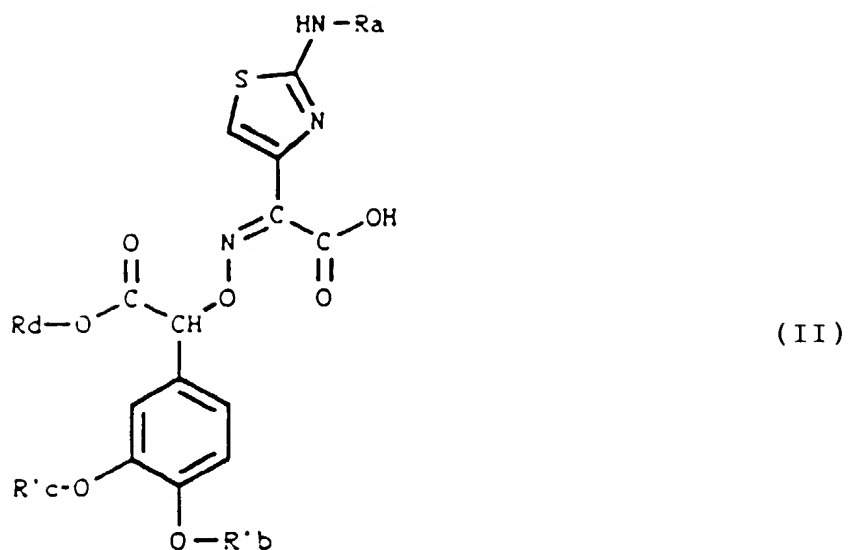


$\text{NH-CO-Q}$ ,  $\text{CN}$ ,  $\text{CH}_2\text{-CN}$ ,  $\text{CH}_2\text{-SQ}$  in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol ) indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 members.

$R_b$  and  $R_c$ , identical or different, represent a hydrogen atom or an acyl group, chosen from the acetyl, propionyl and benzoyl radicals,

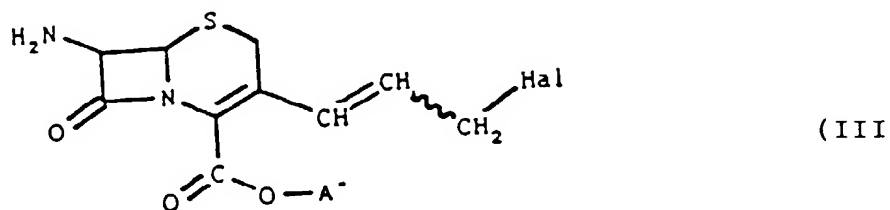
A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or  $\text{CO}_2\text{A}$  represents  $\text{CO}_2$ ; the wavy line means that the  $\text{CH}_2\text{R}_1$  group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids, characterized in that a product of formula (II):





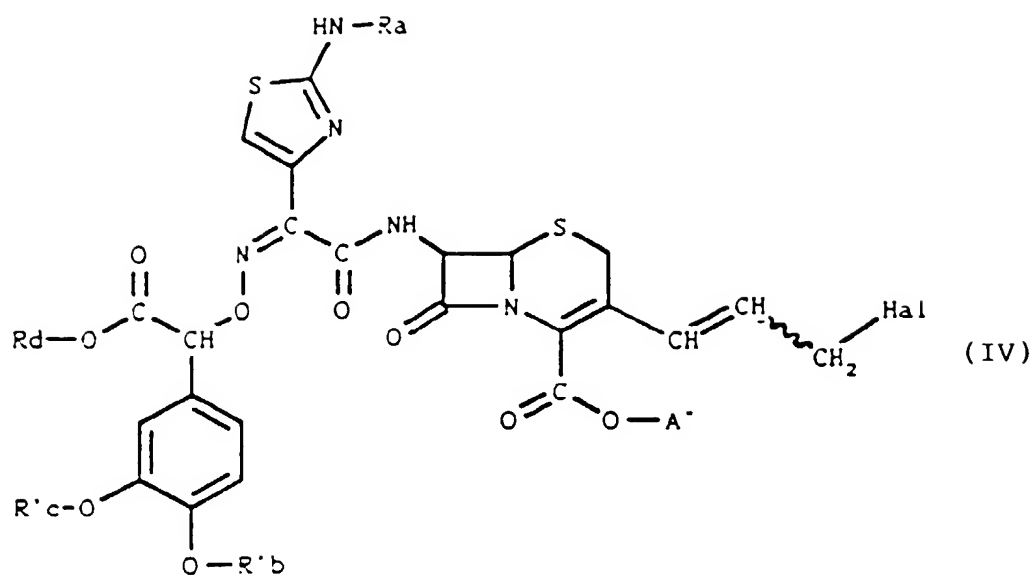
25

racemic or optically active syn isomer or a functional derivative of the product of formula (II), in which  $R_a$  represents a hydrogen atom or a protective group of the amino radical,  $R'_b$  and  $R'_c$ , identical or different, represent a hydrogen atom or a protective group of the hydroxyl radical,  $R_d$  represents a hydrogen atom or the remainder of an easily eliminable ester group, is reacted with a product of formula (III):

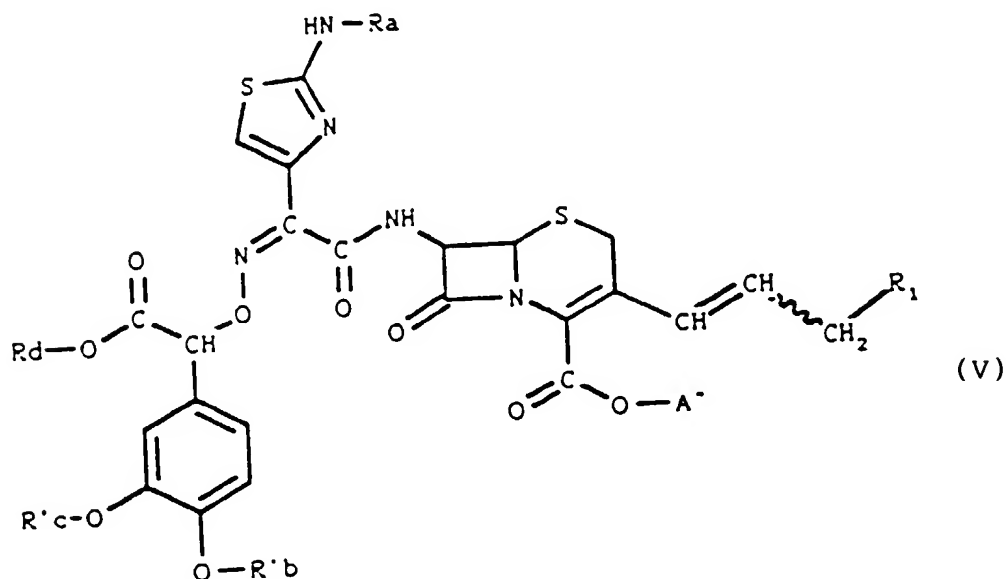


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in which Hal represents a halogen atom,  $A^-$  represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the  $CH_2Hal$  group can be found in E or Z position, in order to obtain a product of formula (IV):



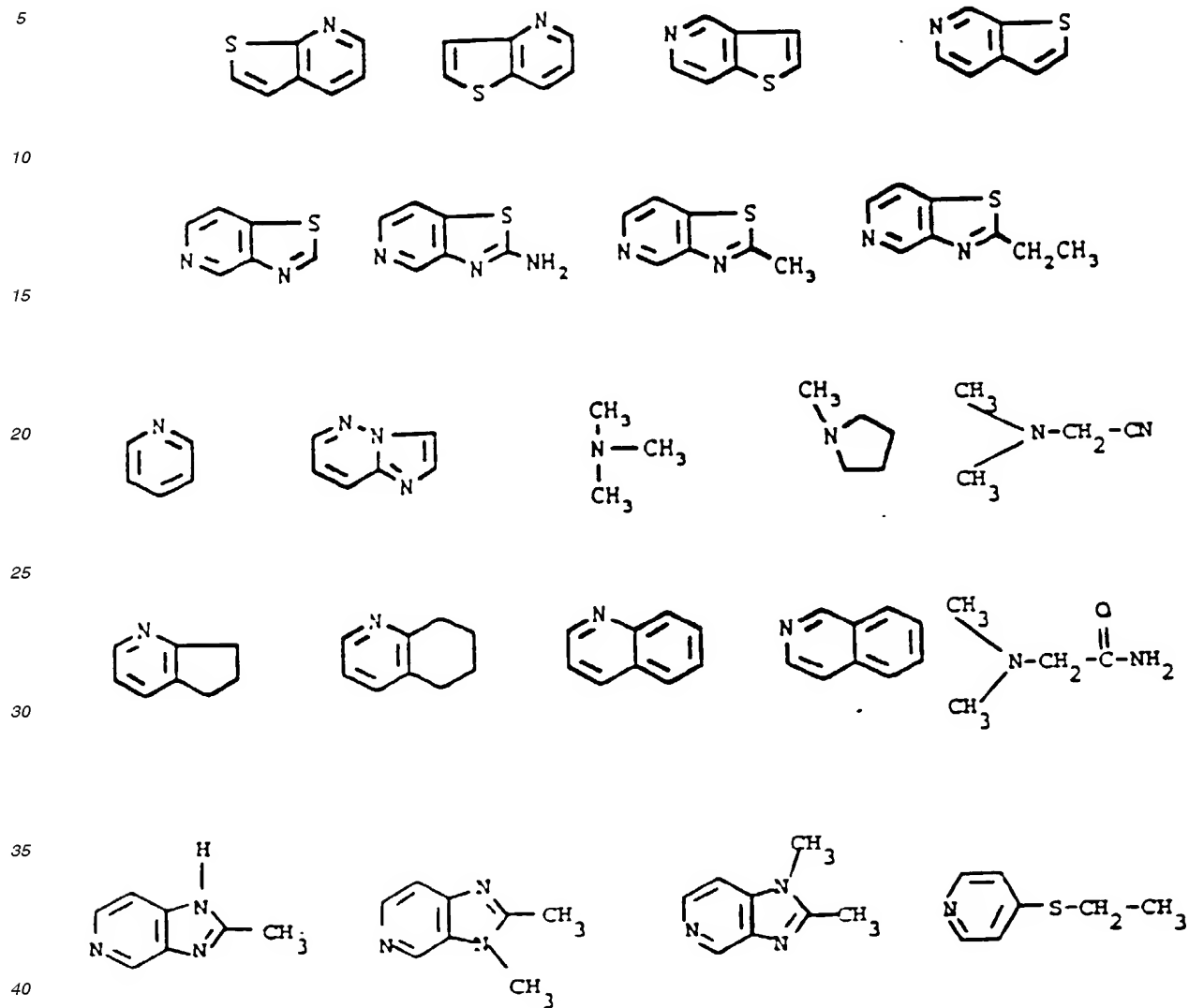
25 which is reacted with a reagent capable of introducing the  $\text{R}_1$  radical in order to obtain a product of formula (V):



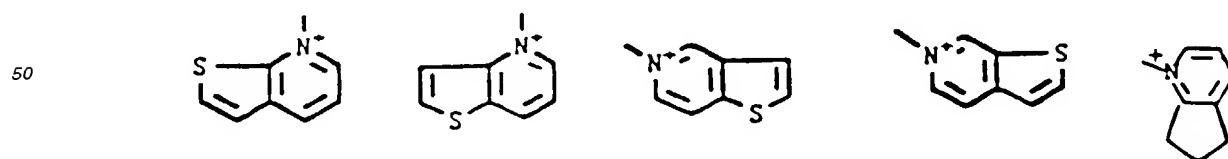
50 which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

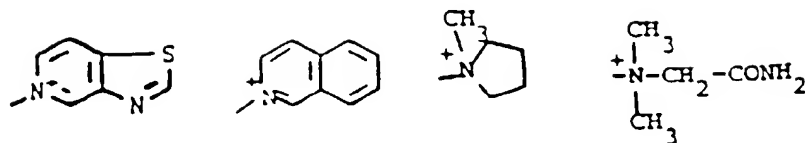
- 55
- a) cleaving, by hydrolysis or by the action of thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,
  - b) esterification or salification of the carboxylic radical or radicals by a base,
  - c) salification of the amino radical by an acid,
  - d) separation of products in the form of an R, S mixture into R or S.

2. Preparation process according to claim 1 characterized in that the reagent capable of introducing the  $R_1$  radical is chosen from the reagents of formulae:

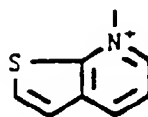


3. Preparation process according to claim 1 or 2, characterized in that the reagent capable of introducing the  $R_1$  radical is chosen from the reagents:

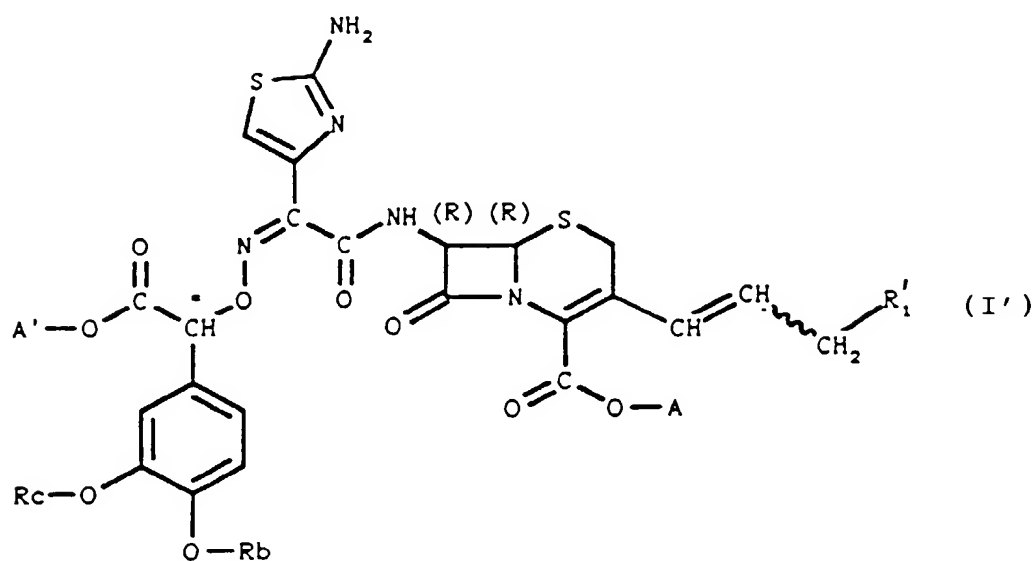




preferably:



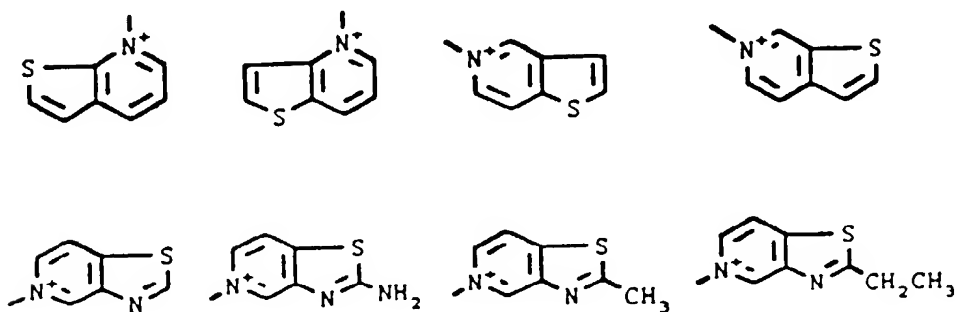
4. Process according to claim 1 for the preparation of the products of formula (I) as defined in claim 1 corresponding to formula (I'):



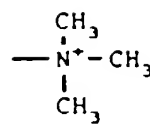
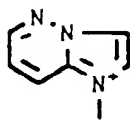
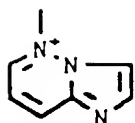
SYN isomer

syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

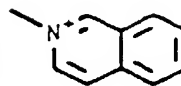
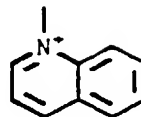
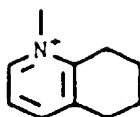
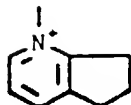
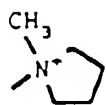
A, A' R<sub>b</sub> and R<sub>c</sub> retain their previous meaning and R'<sub>1</sub> represents a radical chosen from the following radicals:



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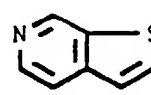
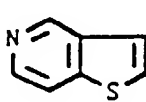
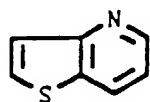
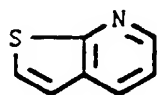
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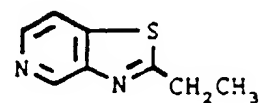
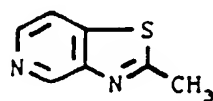
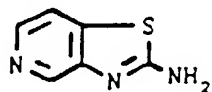
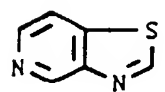
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as well as the salts of the products of formula (I') with mineral or organic acids, characterized in that a product of formula (II) is reacted with a product of formula (III) defined as in claim 1, then a reagent chosen from the reagents of formula:

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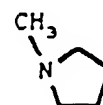
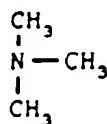
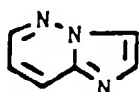


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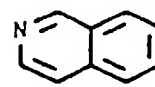
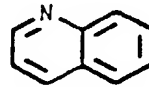
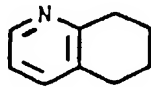
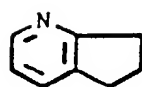


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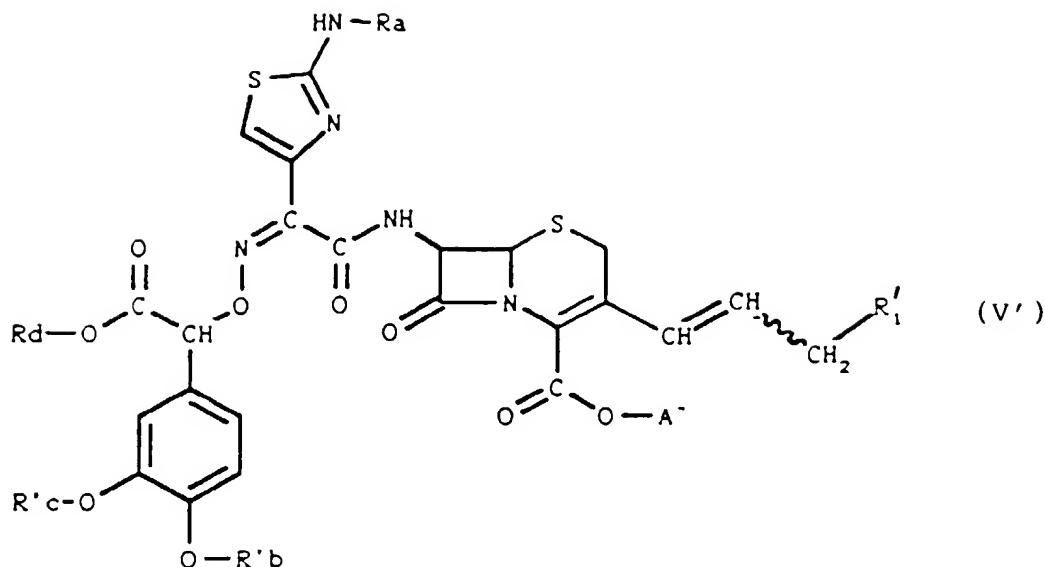


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is reacted with the product of formula (IV) obtained, in order to obtain a product of formula (V'):

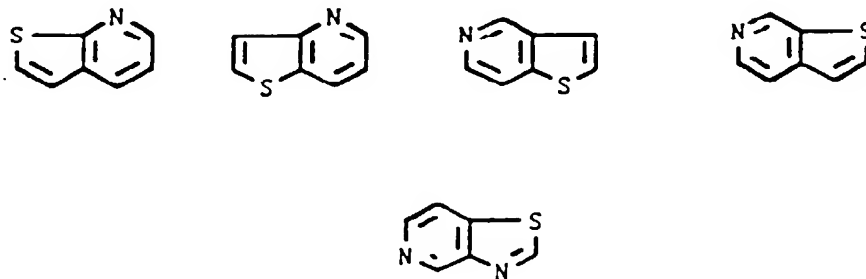
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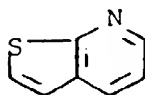
25 which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

- 30 a) cleaving, by hydrolysis or by the action of thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,  
 b) esterification or salification of the carboxylic radical or radicals by a base,  
 c) salification of the amino radical by an acid,  
 d) separation of products in the form of an R, S mixture into R or S.

- 35 5. Process according to claim 4, characterized in that the reagent used on the product of formula (IV) is chosen from the reagents:



50 preferably:



6. Process according to any one of claims 1 to 5, characterized in that the starting products and the reagent used are chosen so as to prepare:

- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,
- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in the R or S form or the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-[[2-amino-4-thiazolyl]-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4, 2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters.

7. Preparation process for pharmaceutical compositions characterized in that at least one of the derivatives of formula (I) as defined in claim 1, as well as their salts with pharmaceutically acceptable acids, is used as active ingredient in a form intended for this use.
8. Preparation process for pharmaceutical compositions characterized in that at least one of the derivatives of formula (I') as defined in claim 4, as well as their salts with pharmaceutically acceptable acids, is used as active ingredient in a form intended for this use.
9. Preparation process for pharmaceutical compositions characterized in that at least one of the derivatives of formula (I) as defined in claim 6, as well as their salts with pharmaceutically acceptable acids, is used as active ingredient in a form intended for this use.
10. As industrial products, the products of formula (IV) and the products of formula (V) in which R<sub>a</sub> represents a protective group of the amino radical, formulae (IV) and (V) being as defined in claim 5.

⑫ **EUROPEAN PATENT APPLICATION**

⑲ Application number: **88306584.9**

⑤① Int. Cl.<sup>4</sup>: **C07D 473/34 , C07D 471/04 ,  
A61K 31/52 , A61K 31/44**

⑳ Date of filing: **19.07.88**

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④③ Date of publication of application:  
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⑦① Applicant: **MERCK & CO. INC.**  
**126, East Lincoln Avenue P.O. Box 2000**  
**Rahway New Jersey 07065-0900(US)**

⑦② Inventor: **Johnston, David B. R.**  
**53 Round Top Road**  
**Warren New Jersey 07060(US)**  
Inventor: **Tolman, Richard L.**  
**29 Upper Warren Way**  
**Warren New Jersey 07060(US)**  
Inventor: **Mac Coss, Malcolm**  
**48 Rose Court**  
**Freehold New Jersey 07728(US)**  
Inventor: **Marburg, Stephen**  
**50 Concord Avenue**  
**Metuchen New Jersey 08840(US)**  
Inventor: **Meurer, Laura C.**  
**620 Ayres Avenue**  
**North Plainfield New Jersey 07060(US)**

⑦④ Representative: **Hesketh, Alan, Dr.**  
**European Patent Department Merck & Co.,**  
**Inc. Terlings Park Eastwick Road**  
**Harlow Essex, CM20 2QR(GB)**

⑤④ **Piperazinyl derivatives of purines and isosteres thereof as hypoglycemic agents.**

⑤⑦ There are disclosed certain 6-piperazino-purine and heteroaromatic derivatives thereof which have oral hypoglycemic activity and with such ability to lower blood sugar are useful in the treatment of type II diabetes and/or obesity with associated insulin resistance. Processes for the preparation of such compounds and compositions containing such compounds as the active ingredient thereof are also disclosed.

**EP 0 300 726 A1**



## PIPERAZINYL DERIVATIVES OF PURINES AND ISOSTERES THEREOF AS HYPOGLYCEMIC AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our copending application Serial Number 75362 filed 20 July 1987.

BACKGROUND OF THE INVENTION

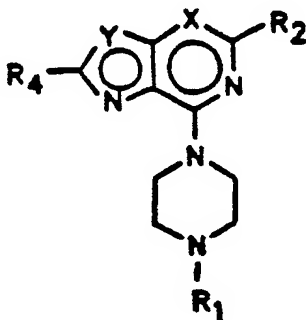
Certain 6H-7,8-dihydrothiapyrano[3,2-d]pyrimidines are disclosed in Belgian Patent 724745 as intermediates for the preparation of compounds with cardiovascular and coronary dilation activity. however, suggestion is made neither of any hypoglycemic activity nor of weight reducing properties for either the intermediates or the final products. Great Britain 2119368 discloses 6H-7,8-dihydrothiapyrano[3,2-d]pyrimidines (where the bicyclic system is not heteroaromatic) with a very different substitution pattern on the nucleus when compared with the instant heteroaromatic compounds.

SUMMARY OF THE INVENTION

The instant invention is concerned with novel 6-piperazinopurines and heteroaromatic derivatives thereof, which are useful as hypoglycemic and/or weight reducing agents. Thus, it is an object of this invention to describe such compounds. It is a further object of this invention to describe the hypoglycemic activity of such compounds. A still further object is to describe compositions containing such compounds as the active ingredient thereof. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The 6-piperazinopurines of this invention are novel compounds with significant hypoglycemic activity. The compounds have the following structures:



wherein X and Y have the following meanings:

X	Y
N-(R <sub>3</sub> ) <sub>m</sub>	N-(R <sub>3</sub> ) <sub>n</sub>
C-R <sub>3</sub>	N-R <sub>3</sub>
N	S
N	O

and  $R_1$  and  $R_3$  are independently hydrogen, loweralkyl, cycloloweralkyl, loweralkenyl, loweralkoxyloweralkyl, loweralkenyl, loweralkynyl, phenylloweralkyl or substituted loweralkyl where the substituent is from 1 to 3 of halogen, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, loweralkylamino or diloweralkylamino, or the substituent is one of a 5- or 6-membered heteroaromatic ring system with nitrogen, oxygen or sulfur as the heteroatom, in particular where the hetero aromatic ring system is pyridyl, furyl or thienyl, and m and n are 0 or 1 such that when m is 0, n is 1 and when m is 1, n is 0;

$R_2$  and  $R_4$  are independently hydrogen, loweralkyl, cycloloweralkyl, loweralkoxy, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, loweralkenyl, loweralkenyloxy, loweralkynyl, mono, di, or trihaloloweralkyl, phenyl or substituted phenyl where the substituent is from 1 to 3 of halo or loweralkyl, phenylloweralkyl, amino, loweralkylamino or dialkylamino where the alkyl group can be linear, branched or joined in a ring of 5- or 6-members optionally containing oxygen or nitrogen as a heteroatom and the pharmaceutically acceptable salts thereof.

The loweralkyl groups of this invention may contain from 1 to 6 carbon atoms and may be in either a linear or branched configuration. Exemplary of such groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, pentyl, hexyl, and the like.

The loweralkoxy groups of this invention may contain from 1 to 6 carbon atoms and may be in either a straight or branched configuration. Exemplary of such groups are methoxy, ethoxy, propoxy, butoxy, isobutoxy, pentoxy, hexoxy, and the like.

The loweralkenyl and loweralkynyl groups of this invention may contain from 2 to 6 carbon atoms and may be in either a linear or branched configuration. Exemplary of such groups are ethenyl, vinyl, butenyl, butynyl, propenyl, propargyl and the like.

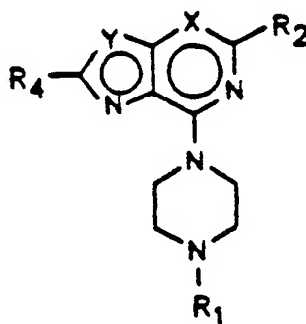
The cycloloweralkyl groups of this invention may contain from 3 to 6 carbon atoms and are exemplified by cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The halogen atoms of this invention may contain any of the halogen fluorine, chlorine, bromine or iodine.

The amino and substituted amino groups are exemplified by amino, methylamino, dimethylamino, ethylamino, diethylamino, pyrrolidino, morpholino, propylamino, and the like.

The preferred compounds of this invention are those wherein  $R_1$  is hydrogen, methyl, ethyl or 2-propenyl;  $R_2$  is hydrogen, methyl, ethyl, methoxy, ethoxy, amino, methylamino, dimethylamino, pyrrolidino or ethylamino; each  $R_3$  is independently hydrogen, methyl, ethyl, n-propyl, i-propyl, methoxymethyl, methoxyethyl, or fluoroethyl, in particular, a halogenated branched loweralkyl group, in particular a halogenated isopropyl, more preferred as a fluorinated isopropyl, and most preferred as 1,3-difluoro isopropyl; and each  $R_4$  is independently hydrogen, methyl, methylamino or dimethylamino.

Further preferred compounds of this invention are realized in the following structural formula:



wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are as defined above, Y is S or N- $R_3$  and the corresponding X is N or C- $R_3$ .

Further preferred compounds are realized in the purine compounds when X and Y are independently N and N- $R_3$ .

In addition, those compounds where  $R_1$  is hydrogen or methyl;  $R_3$  is as defined above, and  $R_2$  and  $R_4$  are independently hydrogen, methyl, methoxy, ethoxy or dimethylamino are particularly preferred.

The most preferred compounds are those wherein  $R_1$  is hydrogen,  $R_2$  is methyl, methoxy or ethoxy,  $R_3$  is as defined above,  $R_4$  is hydrogen, X is N and Y is N- $R_3$ .

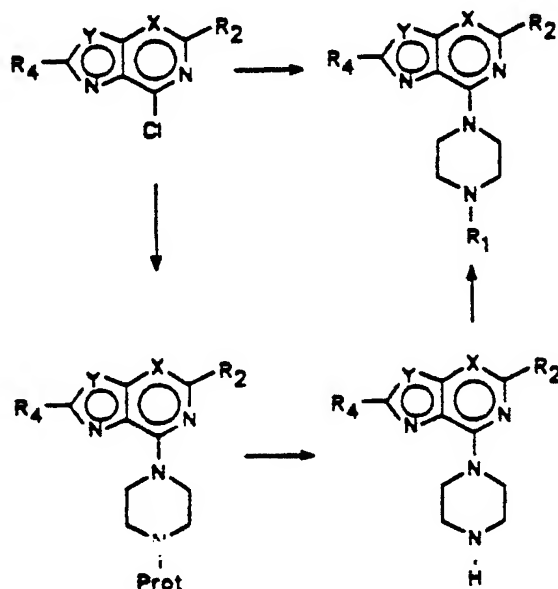
With the presence of various amino groups, it will be appreciated that the instant compounds will be basic in nature and will be capable of forming acid addition salts with acidic compounds. The pharmaceutically acceptable acid addition salts of the compounds of this invention are included within the ambit of this invention. Examples of such pharmaceutically acceptable acid addition salts are those formed from

inorganic acids such as hydrochloric, hydrobromic, nitric, sulfuric, phosphoric, dialkylphosphoric, or hypophosphorous; and organic acids such as acetic, benzenesulfonic, benzoic, citric, fumaric, gluconic, lactic, malic, maleic, oxalic, pantoic, pantothenic, salicylic, stearic, succinic, tannic, tartaric, and the like.

The instant compounds may also be used in combination with other compounds, in particular combinations with other acid hypoglycemic agents is useful. In particular, the instant compounds may be used in combination with sulfonylurea for beneficial effect.

The instant compounds are prepared according to the following reaction scheme:

SCHEME I



wherein  $X$ ,  $Y$ ,  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are as defined above.

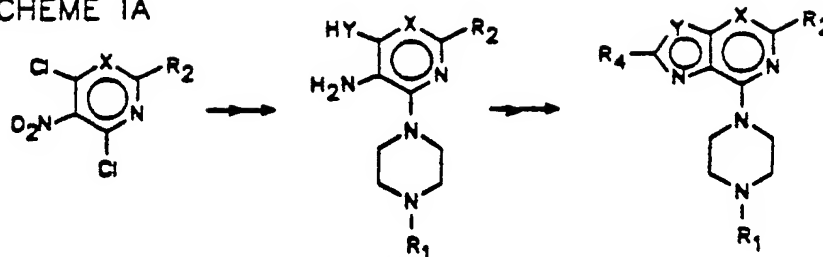
The foregoing reaction is carried out by reacting an  $R_1$ -substituted piperazine with the chloroheterocycle (II). When  $R_1$  is hydrogen the reactant can be a protected piperazine such that only one of the piperazine nitrogen atoms are available for reaction.

The preferred protecting group is the t-butoxycarbonyl (BOC) group. After the protected piperazine has been reacted with the chloroheterocyclic substrate, the protecting group is removed.

The displacement of the chloro by the  $R_1$ -piperazine or protected piperazine is carried out in an optional solvent at a temperature of from 100 to 150 °C such that the solvent does not boil at a temperature less than the desired reaction temperature. The preferred solvents are  $N,N$ -dimethylformamide, ethanol, isoamyl alcohol and the like. It is preferred to carry out the reaction at from about 75 ° to 125 °C and the reaction is generally complete in from about 30 minutes to 16 hours. The reaction proceeds well in the absence of a solvent. The piperazine reagent is generally used in at least 1 molar excess in order to neutralize the hydrogen chloride liberated during the course of the reaction. Preferably 4 equivalents of the piperazine compound are employed. Optionally, the use of a tertiary amine such as triethylamine can be used to reduce the amount of piperazine compound employed in the reaction. The products are isolated from the reaction mixture using standard techniques.

The reactions used to prepare the instant compounds are generally carried out with the displacement of the halogen by the  $R_1$ -piperazine as the last step. However, the  $R_1$  group can be introduced on the unsubstituted piperazine after the piperazine has been placed on the heterocycle and after the removal of the protecting group. Similarly, the reactions used to prepare the heterocycle can include the substitution of the piperazine group prior to the final synthetic steps such as the heterocyclic ring closure or the substitution of the  $R_2$ ,  $R_3$  and  $R_4$  groups (See Scheme 1A).

SCHEME 1A



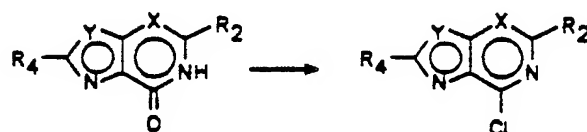
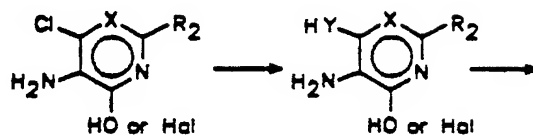
## Early Introduction of Piperazine

Occasionally, the presence of more than one reaction site may result in the preparation of a mixture which will be separated in order to obtain the instant compounds. The various procedures available to those skilled in the art for the preparation of the instant compounds are outlined below and in the appended examples.

The Preparation of 6-(1-piperaziny)-Substituted Purines

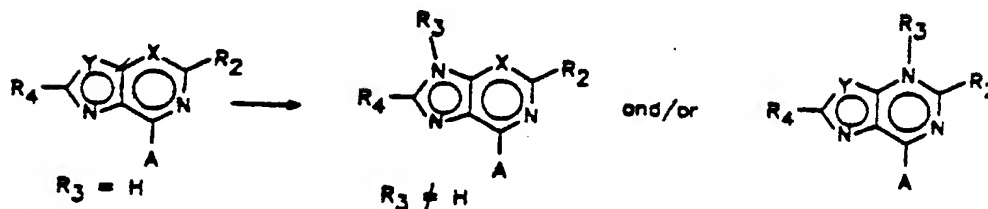
Alkylation with  $R_3$ -Z (Z = leaving group) of a 6-chloropurine with ensuing replacement of chlorine by a protected piperazine followed by deprotection

## SCHEME II



H or Alkyl Substituents in  $R_2$  and/or  $R_4$

## SCHEME III

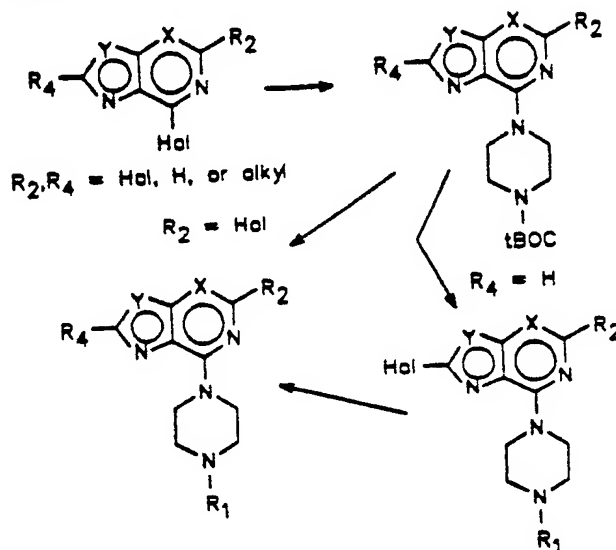


A = halogen or sub'd-piperazine

Transformation of 6-chloropurine to 6-[1-(4-protected)piperazinyl]purine followed by alkylation and deprotection.

Scheme IV

SCHEME IV



### Electronegative Elements in $R_2$ and/or $R_4$

Diabetes is a condition characterized by abnormal insulin secretion and a variety of metabolic and vascular manifestations reflected in a tendency toward inappropriately elevated blood glucose levels and which if left poorly treated or untreated can result in accelerated, nonspecific atherosclerosis, neuropathy and thickened capillary lamina causing renal and retinal impairment. Diabetes is characterized as being insulin dependent (Type I) and non-insulin dependent (Type II). Type I diabetes is due to damage and eventual loss of the  $\beta$ -cells of the pancreatic islets of Langerhans with a resulting loss of insulin production. Type II diabetics secrete insulin, however, the insulin is somehow not properly or effectively utilized in the metabolism of blood sugars and glucose accumulates in the blood to above normal levels. This condition is termed insulin resistance.

With the certainty of serious complications resulting from high glucose levels in poorly controlled or uncontrolled diabetics, means to lower blood glucose have been research goals for a considerable period of time. With Type I diabetes glucose control can only be achieved with daily insulin injections. With Type II diabetes glucose control can be effected from a combination of diet and drugs which lower glucose levels. The currently available oral hypoglycemic agents are not completely satisfactory since they may not offer complete blood glucose control or may provide a variety of undesirable side effects or they may elevate insulin concentrations to undesirable and dangerous levels. Thus, the search for improved oral hypoglycemic agents is a continuing one.

As previously indicated, the compounds of this invention are all readily adapted to their therapeutic use as oral hypoglycemic agents, in view of their ability to lower the blood sugar levels of diabetic subjects to a statistically significant degree. For instance, 6-(1-piperazinyl)-9-methylpurine, a typical and preferred agent of the present invention, has been found to consistently lower blood sugar levels and improve glucose tolerance in either fasted or fed diabetic (i.e., hyperglycemic) mice to a statistically significant degree when given by the oral route of administration at dose levels ranging from 1 mg/kg to 100 mg/kg, respectively, without showing any toxic side effects. The other compounds of this invention also produce similar results. In general, these compounds are ordinarily administered at dosage levels ranging from about 1 mg to about

100 mg per kg of body weight per day, although variations will necessarily occur depending upon the condition and individual response of the subject being treated and the particular type of oral pharmaceutical formulation chosen.

Administration over time to obese, insulin resistant mice, resulted in a significant reduction in body weight.

In connection with the use of the compounds of this invention for the treatment of diabetic subjects, it is to be noted that they may be administered either alone or in combination with other oral hypoglycemic agents in pharmaceutically acceptable carriers and that such administration can be carried out in both single and multiple dosages. More particularly, the novel compounds of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the forms of tablets, capsules, lozenges, troches, hard candies, powders, aqueous suspension, elixirs, syrups and the like. Such carriers include diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical compositions can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for just such a purpose. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include the high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

The activity of the compounds of the present invention, as hypoglycemic agents, is determined by their ability to lower blood sugar levels in the fasted or fed hyperglycemic mouse when tested therein for such purposes according to the procedures described by Saperstein *et al.* as submitted to the journal *Diabetes* and summarized as follows:

Genetically obese mice (ob/ob) were fasted overnight. The compounds were administered orally via a stomach tube and each mouse serially bled from the orbital sinus at various times and the blood samples were analyzed for blood glucose. When the effects of the compounds on blood glucose levels of fed mice were to be determined, glucose was administered orally at a rate of 2 g per kg, 30 minutes after administration of the test compound. Glucose in the blood was determined by the potassium ferricyanide potassium ferrocyanide oxidation reaction auto analyzer.

The latter method measures directly the amount of glucose in the blood at any given time and from this, the maximum percent decrease in blood sugar can be readily calculated and reported as hypoglycemic activity *per se*. In this way, the present compounds are shown to markedly improve glucose tolerance of non-anesthetized hyperglycemic mice when administered to them at dose levels as low as 10 mg/kg orally and lower fasting blood glucose levels when administered at dose levels as low as 30 mg/kg orally.

The instant invention is further described by the following examples which are intended to be merely descriptive and should not be construed as limitative of the invention.

#### EXAMPLE 1

##### 6-[1-(4-tert-butoxycarbonyl)piperazinyl]purine

6-Chloropurine (4.6 g, 30 mmol) and 11.2 g (60 mmol) of N-(1-tert-butoxycarbonyl)piperazine (BOC-piperazine) were dissolved in dimethylformamide (DMF) (150 ml) and the solution was stirred overnight at 100°C under nitrogen (N<sub>2</sub>). The reaction mixture was then evaporated to dryness *in vacuo* and the residue

crystallized from n-propanol affording 5.0 g (55% of 6-[1-(4-BOC)piperazinyl]purine, m.p. 244-246 ° C.

Calc'd for  $C_{14}H_{20}N_6O_2$ :

C, 55.26; H, 6.58; N, 27.63

Found:

5 C, 55.23; H, 6.48; N, 27.63

## EXAMPLE 2

### 6-[1-(4-BOC)piperazinyl]-9-methylpurine

#### Method A

20 To 6-[1-(4-BOC)piperazinyl]purine (1.6 g, 5.58 mmol) dissolved in 60 ml of dimethylsulfoxide (DMSO) was added potassium carbonate (848 mg, 6.14 mmol) and methyl iodide (0.70 ml, 11.2 mmol). The mixture was stoppered and stirred at room temperature for 24 hours at which time an additional 0.35 ml (5.6 mmol) of methyl iodide was added. Stirring was continued for an additional 24 hours and then the reaction mixture was quenched in water. The aqueous mixture was extracted with ethyl acetate. The organic layer was dried

25 with  $Na_2SO_4$  and evaporated to dryness affording 1.3 g of a mixture of 9- and 7- isomers. These were separated on a 100 ml silica gel column using a 90:10 ethyl acetate:ethanol mixture as eluent. The first peak after concentration afforded 1.0 g (56%) of 6-[1-(4-BOC)piperazinyl]-9-methylpurine, m.p. 129-131 ° C.

Calc'd for  $C_{15}H_{22}N_6O_2$ :

C, 56.60; H, 6.92; N, 26.42

30 Found:

C, 56.10; H, 6.78; N, 26.11

#### Method B

35 To 4.5g (26.7 mmol) of 6-chloro-9-methyl purine dissolved in 70 ml of sieve dried, degassed, DMF (dimethylformamide) was added 4.966 g of BOC-piperazine (26.7 mmol) and 4.6 ml of diisopropylethylamine (26.7 mmol). The solution was stored, under  $N_2$ , at 100 ° C for 16 hrs., after which it was evaporated to dryness in vacuo. The orange residue was triturated with warm water (100 ml). The process was repeated and neither water layer showed product (t.l.c.). The residue was dissolved in boiling methanol charcoaled (10% by weight), and after filtration through celite, evaporated to dryness. The residue was dissolved in 95:5 ethyl acetate:ethanol and adsorbed onto 15 ml of silica gel. This was added to the top of a 250 ml silica gel column (dry column) and eluted with 250 ml of 95:5 ethyl acetate:ethanol and then a

40 90:10 mixture. 100 ml fractions were collected and the product which is eluted in fractions 7 to 13. The t.l.c. (9:1 ethyl acetate: ethanol): a single spot shows no BOC piperazine. Recrystallization was effected with acetonitrile affording 7g of 6-[1-(4-BOC)piperazinyl]-9-methylpurine, m.p 129-131 ° C.

Calc'd for  $C_{15}H_{22}N_6O_2$ :

C, 56.60; H, 6.92; N, 26.42.

50 Found:

C, 55.76; H, 6.71; N, 25.98.

## EXAMPLE 3



6-[1-(4-BOC)piperazinyl]-3-methylpurine

The second peak from the above chromatography in Example 2, Method A, after concentration afforded 83 mg (5%) of 6-[1-(4-BOC)piperazinyl]-3-methylpurine, m.p. 235-238 °C.

EXAMPLE 46-(1-piperazinyl)-9-methylpurine

6-[1-(4-BOC)piperazinyl]-9-methylpurine (2.5 g, 8.09 mmol) was dissolved in 50 ml of trifluoroacetic acid (TFA) and the solution aged for 1 hour at room temperature. The TFA was removed in a stream of N<sub>2</sub> and the residue dissolved in 2N HCl (20 ml) and the acidic solution evaporated to dryness in vacuo. This HCl treatment was repeated twice and the final residue crystallized from methanolacetonitrile affording 1.71 g (73%) of 6-(1-piperazinyl)-9-methylpurine dihydrochloride, m.p. 300 °C.

Calc'd for C<sub>10</sub>H<sub>15</sub>N<sub>6</sub>Cl<sub>2</sub>:

C, 41.23; H, 5.50; N, 28.87; Cl, 24.40

Found:

C, 41.33; H, 5.50; N, 28.70; Cl, 24.37

U.V. (H<sub>2</sub>O)λ<sub>max</sub> = 274 (ε = 21,454)

λ<sub>min</sub> = 230; other λ<sub>max</sub> = 218 (ε = 19,283)

EXAMPLE 5N-t-Butoxycarbonyl-N'-benzyloxycarbonylpiperazine

To 15 g of BOC-piperazine (80.6 mmol) dissolved in acetone (50 ml) was added in alternating portions benzylchloroformate (11.5 ml, 80.6 mmol) and 1N NaOH (15 ml) keeping the pH at 8-8.5 and the temperature 0-5 °C. After 2 hours, starting material was still present (tlc) and an additional quantity of benzylchloroformate (5 ml) and 1N NaOH (5 ml) was added. The reaction mixture was aged at 5 °C overnight and at room temperature an additional 7 hours. Water was added and the mixture extracted with ethyl acetate (3 x 50 ml), dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to 21 g of an oil. This oil was dissolved in 10 ml of ethyl acetate, passed through 40 ml of silica gel and eluted with 200 ml of ethylacetate. Crystallization was effected by titration with petroleum ether and the crystals collected, affording 8.28 g (32%) of N-t-butoxycarbonyl-N'-benzyloxycarbonylpiperazine, m.p. 90.5 - 91.5 °C.

Calc'd for C<sub>17</sub>H<sub>24</sub>H<sub>2</sub>O<sub>4</sub>:

C, 63.75; H, 7.50; N, 8.75

Found:

C, 63.53; H, 7.48; N, 8.93

NMR (CDCl<sub>3</sub>, δ from TMS) δ 1.45 (s, 9), δ 3.45 (m, 8), δ 5.12 (s, 2), δ 7.3 (m, 5).

EXAMPLE 6

N-Benzyloxycarbonylpiperazine (CBZ-piperazine)

960 mg (3 mmol) of N-butoxycarbonyl-N'-benzyloxycarbonylpiperazine was dissolved in 8 ml of TFA and aged for 1 hour. The TFA was evaporated in a stream of N<sub>2</sub> and then to the residue was added water and NaOH to pH12. The basic mixture was extracted with 3 x 15 ml of ethyl acetate, backwashed with saturated aqueous NaCl, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to 566 mg of an oil whose mass spectrum had a patent peak at m/e = 220N MR (CDCl<sub>3</sub>,  $\delta$  from TMS)  $\delta$  2.8 (m, 4),  $\delta$  3.5 (t, 4),  $\delta$  5.12 (s, 2),  $\delta$  7.38 (m, 5).

EXAMPLE 79-(1- $\beta$ -Ribofuranosyl)-6-[1-(4-benzyloxycarbonyl)piperazinyl]purine

6-Chloropurine riboside (237 mg, 0.834 mmol) and 410 mg (1.86 mmol) of CBZ-piperazine were dissolved in 12 ml of DMF and heated at 100°C for 20 hours. The mixture was then concentrated to dryness in vacuo affording 854 mg of a residue. This was chromatographed on silica gel (60 ml) eluting with equal volumes of methylene chloride, 2% ethanol in methylene chloride (v/v) and finally with 40% ethanol in methylene chloride (v/v) evaporation of appropriate fractions afforded 320 mg (82%) of 6-[1-(4-CBZ)-piperazinyl]purine riboside.

EXAMPLE 89-(1- $\beta$ -D-Ribofuranosyl)-6-(1-piperazinyl)purine

9-(1- $\beta$ -D-ribofuranosyl)-6-[1-(4-CBZ)piperazinyl]purine (300 mg, 0.64 mmol) dissolved in 10 ml of ethanol was hydrogenated overnight under 40 psi of hydrogen in the presence of 50 mg 10% palladium on charcoal. The reaction mixture was filtered through diatomaceous earth and evaporated to 221 mg of crude product. This was recrystallized three times from ethanol-ether to afford 70 mg of 6-(1-piperazinyl)purine riboside.

Calc'd for C<sub>14</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub>•0.5 H<sub>2</sub>O:

C, 48.70; H, 6.09; N, 24.35

Found:

C, 49.01; H, 5.76; N, 24.31

U.V. $\lambda_{\max}$  (H<sub>2</sub>O) 275;  $\epsilon = 1.81 \times 10^4$ ,  $\lambda_{\max}$  215,  $\epsilon = 13.5 \times 10^4$ .

FAB mass spectrum m/e = 337 (M + 1.).

EXAMPLE 96-Chloro-9-methylpurine

To 5.0 g (31 mmol) of 5-amino-4-chloro-6-methylaminopyrimidine suspended in 200 ml of triethyl orthoformate was added 2.6 ml of concentrated HCl and the resultant mixture was stirred overnight at room temperature (r.t.). The white precipitate was then collected, washed with ether which was then combined

with the orthoformate which was concentrated to give pure 6-chloro-9-methylpurine by tlc (thin layer chromatography) (silica, 90:10  $\text{CHCl}_3:\text{CH}_3\text{OH}$ ). The filtered solid was returned to 150 ml ethyl orthoformate, treated with 1.0 ml concentrated HCl and stirred at 60 °C for 18 hours. The solution was evaporated and the solids combined to give 5 g (94%) of 6-chloro-9-methylpurine, m.p. 205-207 °C.

#### EXAMPLE 10

##### 4-[1-(4-BOC)piperaziny]-5,6-diaminopyrimidine

2.0 g (13 mmol) of 6-chloro-4,5-diamino pyrimidine (Lin et al *J. Org. Chem.* 26, 264-265 (1961)) and 10 g (54 mmol) of N-BOC-piperazine was stirred, molten, at 130 °C for 5 hours. Then an additional 2 g of BOC-piperazine were added and heating continued for an additional 2 hours. The t.l.c. (90:10 ethyl acetate: ethanol) showed only small amounts of the pyrimidine reactant. A large fraction of the unreacted BOC-piperazine was removed by sublimation at 100-130 °C and the residue was chromatographed on 800 ml of silica gel eluting with 90:10 ethyl acetate ethanol. There was obtained 1.8 g of 4-[1-(4-BOC) piperaziny]-5,6-diaminopyrimidine. 200 MHz NMR( $\text{CDCl}_3$ ,  $\delta$  from TMS): 1.46(s,9), 3.17(m,4), 3.55(m,4), 8.02(s,1).

#### EXAMPLE 11

##### 6-[1-(4-BOC)piperaziny]-8-methylpurine

To 500 mg (1.7 mmol) of 4-[1-(4-BOC)piperaziny]-5,6-diaminopyrimidine dissolved in 5.2 ml of 2-methoxyethanol was added 271 mg (2.3 mmol) of acetamidine acetate and the mixture was refluxed under nitrogen for 22 hours. At this time an additional 100 mg of acetamidine acetate was added and reflux was continued for an additional 3 hours. The mixture was then partitioned between ethylacetate and water, the organic layer dried and concentrated to 630 mg of crude product. This was chromatographed on 65 ml of silica gel eluting with equal volumes of 95:5, 93:7, 88:12 and 80:20 ethylacetate:ethanol. The NMR spectrum of the fractions eluting after 150 ml (200 mg) showed mostly product [mass spectrum:(fast atom bombardment) m/e = 319(M+H)]. An analytical sample of the title compound was obtained after two recrystallizations from toluene.

Calc'd for  $\text{C}_{15}\text{H}_{22}\text{N}_6\text{O}_2 \cdot 2\text{H}_2\text{O}$ :

C, 55.58; H, 7.04; N, 25.92.

Found :

C, 56.03; H, 6.93; N, 25.47.

uv (methanol):  $\lambda_{\text{max}}$  273 nm.

#### EXAMPLE 12

##### 8-Methyl-6-(1-piperaziny)purine

To 1.6 ml of trifluoroacetic acid (TFA) was added 54 mg (0.17 mmol) of 6-[1-(4-BOC)piperaziny]-8-methylpurine and the solution aged for 1 hour. The TFA was then evaporated in a stream of dry nitrogen and the residue converted to the hydrochloride by dissolving it in 2 ml of 2N HCl and evaporating *in vacuo*. This process was repeated twice. The hydrochloride was recrystallized from methanolacetonitrile affording 34 mg of 8-methyl-6-(1-piperaziny)purine (isolated as hydrated di hydrochloride):

Calc'd: for  $\text{C}_{10}\text{H}_{14}\text{N}_6 \cdot 2\text{HCl} \cdot 0.8\text{H}_2\text{O} \cdot 0.05 \text{ NaCl}$ :

C, 38.91; H, 5.75; N, 27.22; Cl, 23.57.

Found :

C, 39.29; H, 5.55; N, 26.84; Cl, 23.95.

Mass spectrum m/e = 218.

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### EXAMPLE 13

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#### 5-Amino-4-[1-(4-BOC)piperazinyl]-6-methylamino pyrimidine

To a stirred melt of 11 g (59 mmol) of BOC-piperazine at 130 ° C was added 2.06 g (13 mmol) of 5-amino-6-chloro-4-methylaminopyrimidine (Robins et al, JACS, 79, 490-494 (1957)) and the mixture heated at 130 ° C for 6.5 hours. Then after aging at room temperature overnight, the reaction mixture was heated for an additional 48 hours at 130 ° (at 24 hours an additional 2 g of BOC piperazine was added.) Excess BOC piperazine was removed by sublimation and the residue (8 g) was chromatographed on a 600 ml silica gel (dry) column eluting with ethyl acetate. The product (400 mg) elutes with 3.6 to 4.6 L of eluent. Mass spectrum: m/e = 308.300 MHz NMR (CDCl<sub>3</sub>, δ from TMS): 1.45 (s,9), 3.05 (m,7), 3.50 (m,4), 8.14 (s,1).

20

### EXAMPLE 14

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#### 6-[1-(4-BOC)piperazinyl]-8,9-dimethylpurine

To 400 mg (1.29 mmol) of 5-amino-4-[1-(4-BOC) piperazinyl]-6-methylaminopyrimidine dissolved in 2 ml of 2-methoxyethanol was added 305 mg (2.58 mmol) of acetamidine acetate and the mixture refluxed for 24 hours and then aged for an additional 16 hours at room temperature. The solution was then quenched into H<sub>2</sub>O and extracted with ethylacetate. The organic layer was dried over sodium sulfate and concentrated to 474 mg of a mixture. This was chromatographed on 105 g of silica gel with a chloroform-methanol step gradient [from 100% chloroform to 92% (v/v) chloroform: 8% methanol]. The product was identified by t.l.c. and recrystallized three times from cyclohexane affording 77 mg of 6-[1-(4-BOC)piperazinyl]-8,9-dimethylpurine.

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### EXAMPLE 15

#### 8,9-Dimethyl-6-(1-piperazinyl)purine

6-[1-(4-BOC)piperazinyl]-8,9-dimethyl purine (75 mg, 0.25 mmol) was dissolved in 2.0 ml of trifluoroacetic acid (TFA) and the solution aged at room temperature for 1 hour. The TFA was then evaporated in a stream of dry nitrogen and the residue converted to the hydrochloride by three times dissolving it in 2 ml of 2N HCl and concentrating to dryness. The crude hydro chloride was recrystallized from methanol-acetonitrile affording 59 mg (82%) of 8,9-dimethyl-6-(1-piperazinyl)purine.

50

Calc'd for: C<sub>11</sub>H<sub>16</sub>N<sub>6</sub>•2HCl•0.3H<sub>2</sub>O:

C, 42.31; H, 5.96; N, 26.92; Cl, 22.76.

Found :

55 C, 42.30; H, 5.88; N, 26.80; Cl, 23.03

mass spectrum (EI) m/e 232.

EXAMPLE 16Imidazo[4,5-c]pyridine(3-deazapurine)

To 5.0 of 3,4-diaminopyridine (Aldrich, 45.82 mmol) suspended in 45 ml of 2-methoxyethanol was added 6.4 g of formamidine acetate (Aldrich, 61.5 mmol) and the mixture heated at reflux (it becomes a solution) for 16 hrs. The solution was then evaporated in vacuo to a solid residue which was recrystallized from 50 ml of acetonitrile. This afforded 4.06 g of imidazo[4,5-c]pyridine (74.5%) m.p. 166-168 °C [lit 162-163 °C, Y. Mizuno, et al. Chem. Phar. Bull., 12, 866-872 (1964)]. 200 MHz NMR (D<sub>2</sub>O, δ from TSP): 7.6 (1H, d, J=6Hz) 8.23 (1H, d, J=6 Hz) 8.30 (1H,s) 8.84 (1H,s).

EXAMPLE 171H-Imidazo[4,5-c]pyridine-5-oxide

1H Imidazo[4,5-c]pyridine (4.0 g, 33.6 mmol) was dissolved in 60 ml of fresh acetic acid, heated to 73 °C ± 1 °C and to the solution was added 8.8 ml of 30% H<sub>2</sub>O<sub>2</sub> (78 mmol). After stirring and heating at 73 °C for 24 hrs, an additional 5 ml of H<sub>2</sub>O<sub>2</sub> was added as well as 1 ml of trifluoroacetic acid. Heating at 73 °C was continued for an additional 3 days. After concentrating, an aliquot NMR (D<sub>2</sub>O) shows a 2:1 product: starting material mixture. Concentration of the main reaction mixture was followed by trituration of the residue with 50 ml of acetonitrile. The filtered insolubles 1.6 g (35%) are pure N-oxide by TLC, (reverse phase, 9:1 H<sub>2</sub>O:THF) 200 MHz NMR (D<sub>2</sub>O, δ from TSP): 7.82 (1H, d, J=7 Hz) 8.21 (1H, d of d, J=7Hz, J=1 Hz) 8.52 (1H, s) 8.84 (1H, d, J=1).

A second crop of 0.8 g is obtained by aging at 4 °C.

EXAMPLE 184-Chloroimidazo-(4,5-c)pyridine

2.84 g (21 mmol) of imidazo(4,5-c)pyridine-5-oxide was dissolved in 200 ml of freshly distilled POCl<sub>3</sub> and refluxed for 16 hrs. The insolubles (starting material, approx. 0.8 g) were filtered and the excess POCl<sub>3</sub> was then removed by distillation and the residue was dissolved in 30 ml of H<sub>2</sub>O and made basic with concentrated NH<sub>3</sub> to pH 8. The solution was extracted 3 times with 30 ml of isoamyl alcohol. This was backwashed with 1 ml of H<sub>2</sub>O and concentrated to give 1 g of product. This was dissolved in 5-10 ml of 1:1 ethanol:CHCl<sub>3</sub> and applied to a silica gel column (56 g) packed in 7% ethanol: CHCl<sub>3</sub> and then eluted with 15% ethanol:CHCl<sub>3</sub>. Chromatographically pure material (0.710 g, 22%) was obtained. Based on recovered starting material the yield is 31%. 200 MHz NMR (DMSO, δ from TMS): 7.68 (1H, d, J=6Hz) 8.20 (1H, d, J=6Hz) 8.50 (s, 1H).

EXAMPLE 19

4-[1-(4-BOC)piperazinyl]-1H-imidazo(4,5-c)pyridine

253 mg (1.65 mmols) of 4-chloro-1H-imidazo(4,5-c)pyridine and 1.07 g BOC-piperazine were dissolved in 2 ml of DMF and the solution was heated at 150 °C for 2 hr, aged at room temperature for 16 hrs and then heated an additional 4 hrs at 150 °C. The DMF was removed in vacuo, the residue covered with 7 ml of ethyl acetate, filtered (the solid gives a positive AgNO<sub>3</sub> test) and the resulting filtrate applied to a 14 g silica gel column developed with EtOAc. The first UV positive peak was concentrated to 0.72 g of a mixture. This was rechromatographed on 22 g of silica gel (packed in CHCl<sub>3</sub>) eluting with 250 ml 20:80 EtOAc:CHCl<sub>3</sub>, 250 ml 33:67 EtOAc:CHCl<sub>3</sub>, 250 ml 1:1 EtOAc:CHCl<sub>3</sub> and then with pure EtOAc. Fractions containing the required material were concentrated to give 164 mg of pure product (32%). 300 MHz NMR (CDCl<sub>3</sub>, δ from TMS) 1.5 (9H, s) 3.6 (4H, m), 4.15 (4H, m), 6.76 (1H, d, J = 5 Hz) 7.92 (1H, s) 7.95 (1H, d, J = 5 Hz).

15 EXAMPLE 2020 4-[1-(4-BOC)piperazinyl]-1-methyl-1H-imidazo[4,5-c] pyridine

To 158 mg of 4-piperazinyl-1H-imidazo (4,5-c)pyridine (0.52 mmol) dissolved in 3.8 ml DMF was added 36 mg of 60% NaH/in oil and 0.064 ml of methyl iodide. The mixture was stirred for 6 hrs at room temperature and then quenched into 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. This was washed 5 times with 12 ml of H<sub>2</sub>O, 12 ml of saturated aqueous NaCl and then dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration afforded 187 mg of crude product which was purified by preparative TLC (2x1000μ silica gel plates) developed in 60:50 CH<sub>2</sub>Cl<sub>2</sub>:EtOAc to give 84 mg of pure product.

30 EXAMPLE 2135 1-Methyl-4-(1-piperazinyl)-1H-imidazo(4,5-c)pyridine

The above 84 mg from Example 20 were dissolved in 4 ml of trifluoroacetic acid (TFA), aged for 1 hr at room temperature and then concentrated to an oily residue by evaporation of the TFA in a stream of N<sub>2</sub>. This residue was dissolved in concentrated HCl (2 ml) and the solution evaporated to dryness. The procedure was repeated twice. The product was slurried in 2.5 ml of ethanol:1 ml acetonitrile for 17 hrs, affording pure 4-(1-piperazinyl)-1-methyl-1H-imidazo(4,5-c)pyridine dihydrochloride.

Calcd, for C<sub>11</sub>H<sub>15</sub>N<sub>5</sub> • 2HCl • 0.4 H<sub>2</sub>O:

C, 43.79; H, 6.11; N, 23.21; Cl, 23.50

Found:

45 C, 44.00; H, 6.02; N, 23.00; Cl, 23.40.

200 MHz NMR (D<sub>2</sub>O, δ from TSP): 3.56 (4H, m) 4.40 (4H, m) 7.36 (1H, d, J = 5 Hz) 7.82 (1H, d, J = 5 Hz) 8.28 (1H, s).

50 EXAMPLE 22

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6-[1-(4-BOC)piperazinyl]-8-bromo-9-methylpurine

To 0.3 g of 6-[1-(4-BOC)piperazinyl]-9-methylpurine (0.94 mmol) in 15 ml of dioxane was added 1.5 g  $\text{Na}_2\text{HPO}_4$  followed by 15 ml  $\text{H}_2\text{O}$ . After stirring 15 min, 0.10 ml  $\text{Br}_2$  (0.312 g; 1.95 mmol) was added dropwise and stirring continued for two days. The mixture was extracted five times with 5 ml portions of  $\text{CHCl}_3$ , and the combined extracts washed successively with aqueous  $\text{NaHSO}_3$ , saturated  $\text{NaCl}$ , dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to a yellowish gum. Preparative chromatography on four 20 x 20 cm x 1000  $\mu$  silica GF plates, developed with  $\text{EtOAc}$ , afforded 244 mg of a solid product (0.61 mmol; 65% yield). Recrystallization from  $\text{EtOH}$  gave an analytical sample, mp 151-152° C.

Calculated for  $\text{C}_{15}\text{H}_{21}\text{N}_5\text{OBr}$ :

C, 45.34; H, 5.33; N, 21.16; Br, 20.12.

Found:

C, 45.21; H, 5.38; N, 20.86; Br, 23.46.

EXAMPLE 238-Bromo-9-methyl-6-(1-piperazinyl)purine dihydrochloride

A solution of 100 mg of 6-[1-(4-BOC)piperazinyl]-8-bromo-9-methylpurine (0.25 mmol) in 5 ml absolute  $\text{EtOH}$  was treated with about 1 ml of ethanolic  $\text{HCl}$ . After 15 minutes, a white precipitate began to form. After standing overnight the suspension was filtered, but the product was only partially deblocked. Solids and filtrate, after evaporation were combined in about 1 ml trifluoroacetic acid. After 15 minutes, the mixture was evaporated to a gum and partitioned between chloroform and aqueous 10%  $\text{Na}_2\text{CO}_3$ . The aqueous layer was extracted again with chloroform, the combined extracts dried with  $\text{MgSO}_4$  and evaporated to a gum. The gum was taken up in about 1 ml of absolute  $\text{EtOH}$  and treated with about 1 ml of ethanolic  $\text{HCl}$ . After standing overnight the suspension was filtered, the solid washed successively with  $\text{EtOH}$ ,  $\text{EtOH}/\text{ether}$ , and ether. After drying under a nitrogen stream, 53 mg (0.14 mmol; 56% isolated yield) of a white powder was obtained.

Calculated for  $\text{C}_{10}\text{H}_{13}\text{N}_5\text{Br} \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$ :

C, 30.94; H, 4.42; N, 21.66; Cl, 20.59.

Found:

C, 31.09; H, 4.26; N, 21.54; Cl, 20.27.

EXAMPLE 246-[1-(4-BOC)piperazinyl]-8-bromopurine

To 5.0 g (16 mmol) of 6-[1-(4-BOC)piperazinyl]purine suspended in 250 ml of dioxane was added, with stirring, a solution of 25 g  $\text{K}_2\text{HPO}_4$  in 250 ml water, followed after brief stirring by dropwise addition of 1.7 ml  $\text{Br}_2$  (5.3g; 33 mmol). After about 1 hr, the mix was extracted five times with 100 ml portions of chloroform. The combined extracts were washed successively with aqueous  $\text{NaHSO}_3$ , saturated  $\text{NaCl}$ , dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to give 5.52 g (14.4 mmol) of an orange white solid (90% crude yield). Recrystallization from  $\text{EtOH}$  provided an analytical sample:

Calculated for  $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_2\text{Br}$ :

C, 43.87; H, 5.00; N, 21.93; Br, 20.85.

Found:

C, 44.13; H, 5.12; N, 21.68; Br, 20.76.

EXAMPLE 256-[1-(4-BOC)piperazinyl]-8-methylaminopurine

A glass bomb liner was charged with 0.5 g of 6-[1-(4-BOC)piperazinyl]-8-bromopurine (1.3 mmol), 25 ml MeOH and ca. 10 ml H<sub>2</sub>NCH<sub>3</sub>, sealed, and heated with gentle agitation for 24 hours at 150 °C. The dark mixture that resulted was evaporated to a gum with a N<sub>2</sub>-stream and purified by preparative tlc on four 20 x 20 cm x 1000 µ silica GF plates, developing with 1:10:90-conc. NH<sub>4</sub>OH:MeOH:CHCl<sub>3</sub> to give 204 mg of a brownish gum. This was triturated several times with ether to give 100 mg of a residue which was crystallized from EtOH to give 51 mg (15% yield) of product.

Calculated for C<sub>15</sub>H<sub>23</sub>N<sub>7</sub>O<sub>2</sub>:

C, 54.04; H, 6.95; N, 29.41.

Found:

C, 54.17; H, 7.21; N, 28.61.

EXAMPLE 268-Bromo-6-(1-piperazinyl)purine dihydrochloride

A solution of 250 mg of 6-[1-(4-BOC)piperazinyl]-8-bromopurine (0.65 mmol) in 8 ml abs. EtOH was treated with 1.5 ml ethanolic-HCl and allowed to stand overnight. The resultant suspension was filtered, and the cake washed successively with EtOH, EtOH/ether, and finally ether. The cake was dried by sucking dry under N<sub>2</sub> to give a white powder. A sample dried overnight under high vacuum was submitted for analysis:

Calculated for C<sub>9</sub>H<sub>11</sub>N<sub>5</sub>Br•2HCl:

C, 30.36; H, 3.68; N, 23.60; Br, 22.44; Cl, 19.91.

C, 30.19; H, 3.72; N, 22.66; Br, 20.50; Cl, 19.41.

EXAMPLE 276-Chloro-2,9-dimethylpurine

This was prepared in a manner similar to that described in Example 9 for 6-chloro-9-methylpurine, except that 5-amino-4-chloro-2-methyl-6-methylaminopyrimidine was used as the starting material and the reaction was carried out at 60 °C for 6 hrs. The title compound was obtained in 97% yield.

EXAMPLE 286-[1-(4-BOC)piperazinyl]-2,9-dimethylpurine

6-Chloro-2,9-dimethylpurine (1.0 g; 5.48 mmol) was dissolved in isopentyl alcohol (90 ml) and 1-BOC-piperazine (1.54 g, 8.25 mmol) was added, followed by triethylamine (1.16 ml; 8.25 mmol). This solution was heated under reflux (bath temp 146 °C) overnight. The reaction mixture was evaporated to dryness in vacuo, followed by an additional evaporation from toluene. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and the



solution was extracted with aqueous 10% Na<sub>2</sub>CO<sub>3</sub> solution. The organic layer was dried over MgSO<sub>4</sub>, filtered, and evaporated to dryness. This residue was chromatographed on a column of silica gel 60 (200 g) developed successively with EtOAc (500 ml), EtOAc:MeOH (49:1; 400 ml), EtOAc:MeOH (97:3; 400 ml) and then EtOAc:MeOH (95:5) until completion. Fractions containing the required product were pooled and  
 5 evaporated to dryness to give a residue which crystallized on standing to give the title compound in quantitative yield.

Calculated for C<sub>16</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>:

C, 57.81; H, 7.28; N, 25.28.

Found:

10 C, 57.93; H, 7.30; N, 25.12.

### EXAMPLE 29

#### 6-[1-(4-BOC)piperazinyl]-8-bromo-2,9-dimethylpurine

20 To a solution of 1.66g 6-[1-(4-BOC)piperazinyl]-8-bromo-2,9-dimethylpurine (4.97 mmol) in 90 ml dioxane was added a solution of 9 g K<sub>2</sub>HPO<sub>4</sub> in 90 ml water, followed after brief stirring, by dropwise addition of 0.5 ml Br<sub>2</sub> (1.6 g; 10 mmol). After 5 hours, the mix was extracted five times with 50 ml portions of CHCl<sub>3</sub> and the combined extracts washed with aqueous NaHSO<sub>3</sub>, saturated NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>,  
 25 filtered and evaporated to give 3.5 g of a pinkish gum. Chromatography on 50 g silica gel packed in CHCl<sub>3</sub>, was carried out, eluting with CHCl<sub>3</sub> and then EtOAc:CHCl<sub>3</sub>(1:9). A total of 1.8 g (4.4 mmol; 88% yield) of product, after crystallization from EtOH, was obtained. Recrystallization from EtOH gave material with mp 167-169 °C.

Calculated for C<sub>16</sub>H<sub>23</sub>N<sub>6</sub>O<sub>2</sub>Br:

C, 46.72; H, 5.64; N, 20.43; Br, 19.43.

30 Found:

C, 46.41; H, 5.63; N, 20.14; Br, 19.38.

### EXAMPLE 30

#### 6-[1-(4-BOC)piperazinyl]-2,9-dimethyl-8-methylaminopurine

40 A glass bomb liner was charged with 0.5 g 6-[1-(4-BOC)piperazinyl]-8-bromo-2,9-dimethylpurine (1.2 mmol), 25 ml MeOH and 10 ml H<sub>2</sub>NCH<sub>3</sub>, sealed, and heated at 130 °C for 18 hours with gentle agitation. The recovered solution was concentrated to a gum under a stream of N<sub>2</sub>, and purified on four 20 x 20 cm x 1000 μ silica GF plates, eluting with 0.5:5:95/conc. NH<sub>4</sub>OH:MeOH:CHCl<sub>3</sub> to give 512 mg (1.4 mmol; 94%  
 45 crude yield). Recrystallization from EtOH/ether gave 191 mg of product, m.p. 209-211 °C.

Calculated for C<sub>17</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub>:

C, 56.49; H, 7.53; N, 27.13.

Found:

50 C, 56.64; H, 7.60; N, 27.02.

### EXAMPLE 31

6-[1-(4-BOC)piperazinyl]-2,9-dimethyl-8-dimethylaminopurine

A glass bomb liner was charged with 0.4 g of 6-[1-(4-BOC)piperazinyl]-2,9-dimethyl-8-methylaminopurine (0.97 mmol), 30 ml MeOH, and ca. 10 ml HN(CH<sub>3</sub>)<sub>2</sub>, sealed and heated with gentle agitation for 15 hours. The recovered material was concentrated to an oil under a stream of N<sub>2</sub> and purified on four 20 x 20 cm x 1000 μ silica GF plates, developed with 1:10:90/conc.NH<sub>4</sub>OH:MeOH:CHCl<sub>3</sub>, to give 331 mg (.98 mmol; quantitative) of crude product. Recrystallization from EtOH gave material with mp 157-159 °C.

EXAMPLE 322,9-Dimethyl-8-methylamino-6-(1-piperazinyl)purine dihydrochloride

To 175 mg of 6-[1-(4-BOC)piperazinyl]-2,9-dimethyl-8-methylaminopurine (0.48 mmol) was added ca. 0.5 ml of conc. HCl. The mixture foamed initially, then settled to a slightly cloudy solution. After 1 hour, the reaction mixture was concentrated to 0.3 ml under a stream of N<sub>2</sub> diluted to 2 ml with 95% EtOH and concentration resumed. When crystallization commenced the solution was stoppered and allowed to stand until complete. After filtration, washing successively with EtOH, EtOH/ether, and finally ether, followed by drying in a N<sub>2</sub> stream, 148 mg (0.44 mmol; 92% yield) of product was obtained:

Calculated for C<sub>12</sub>H<sub>19</sub>N<sub>7</sub>•2HCl•1.9H<sub>2</sub>O:

C, 39.10; H, 6.82; N, 26.60; Cl, 19.24.

Found:

C, 39.32; H, 6.74; N, 26.56; Cl, 19.03.

EXAMPLE 336-[1-(4-BOC)piperazinyl]-2,9-dimethyl-8-(1-pyrrolidinyl)purine

A glass bomb liner was charged with 296 mg of 6-[1-(4-BOC)piperazinyl]-8-bromo-2,9-dimethylpurine (0.72 mmol), 25 ml MeOH, and 10 ml pyrrolidine, sealed, and heated at 130 ° for 15 hours with gentle agitation. The recovered material was concentrated under a stream of N<sub>2</sub> and purified on four 20x20 cmx1000 μ silica GF plates developed with 2:120:80/conc.NH<sub>4</sub>OH:MeOH:CHCl<sub>3</sub> to give 0.277 g (0.69 mmol; 95% yield) of crude product. Recrystallization from EtOH gave material with mp. 197-199 °C.

EXAMPLE 346-[1-(4-BOC)piperazinyl]-2,9-dimethyl-8-methoxypurine

A solution of 300 mg 6-[1-(4-BOC)piperazinyl]-8-bromo-2,9-dimethylpurine (0.73 mmol) in 4 ml MeOH was treated with 1 ml of 4M NaOMe in MeOH and then refluxed for 2 hours. After concentration to a gum under a stream of N<sub>2</sub>, the residue was partitioned between aqueous 10% NaHCO<sub>3</sub> and CHCl<sub>3</sub> and the aqueous phase was further extracted four more times with CHCl<sub>3</sub>. The combined organic extracts were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated to a cloudy oil which was purified on four 20x20 cm x1000 μ silica GF plates, developed with 1:1 EtOAc:CHCl<sub>3</sub> to give 200 mg (0.55 mmol; 75% of crude product). Recrystallization from ether gave 127 mg of pure product, mp. 128-129 °C.

EXAMPLE 352,9-Dimethyl-8-dimethylamino-6-(1-piperazinyl)purine dihydrochloride

The procedure used in Example 32 was employed using the corresponding 8-dimethylamino analog (prepared as in Example 31). In this case, the crude product was recrystallized successfully only after excess water was removed by distilling off several portions of absolute EtOH. The final mixture was concentrated and upon standing the product crystallized.

Calculated for  $C_{13}H_{21}N_7 \cdot 2HCl \cdot 1.2H_2O$ :

C, 42.21; H, 6.92; N, 26.51; Cl, 19.17.

Found:

C, 42.18; H, 6.92; N, 26.39; Cl, 18.99.

EXAMPLE 362,9-Dimethyl-6-(1-piperazinyl)-8-(1-pyrrolidinyl)purine dihydrochloride

The process described above in Example 32 was repeated using the 8-(1-pyrrolidinyl) analog (prepared as described in Example 33). As in Example 35, the EtOH azeotropic removal of water was used to encourage crystallization.

Calculated for  $C_{15}H_{23}N_7 \cdot 2HCl \cdot 0.2 H_2O$ :

C, 47.66; H, 6.77; N, 25.95; Cl, 18.76.

Found:

C, 47.80; H, 6.67; N, 25.93; Cl, 18.65.

EXAMPLE 376-[1-(4-BOC)piperazinyl]-8-methoxy-9-methylpurine

A solution of 0.5 g of 6-[1-(4-BOC)piperazinyl]-8-bromo-9-methylpurine (1.26 mmol) in 5.0 ml MeOH was treated with 1.0 ml of 4M NaOMe in MeOH, stirred, and heated under reflux for 1.5 hours. After concentration to a gum under a  $N_2$  stream, the residue was partitioned between 10%  $NaHCO_3$  and  $CHCl_3$ , the aqueous phase was extracted three more times with  $CHCl_3$ , the combined  $CHCl_3$  extracts washed with saturated NaCl and dried over  $Na_2SO_4$ . After filtration and concentration, the residue, 483 mg, was taken up in ether, concentrated to an oil and the process repeated. Finally, the residue was taken up in ether and concentrated by boiling to about 0.8 ml. Upon standing, the product crystallized and, after isolation, weighed 256 mg. (0.74 mmol; 58% yield).

EXAMPLE 38

6-[1-(4-BOC)piperazinyl]-8-dimethylamino-9-methylpurine

A glass bomb liner was charged with 0.4 g of 6-[1-(4-BOC)piperazinyl]-8-bromo-9-methylpurine (1.0 mmol), 30 ml MeOH, and ca. 10 ml HN(CH<sub>3</sub>)<sub>2</sub>, sealed, and heated at 130 °C with gentle agitation for 15 hours. The recovered material was concentrated to an oil under a N<sub>2</sub> stream and purified on four 20x20cmx1000 μ silica GF plates developed with 1:10:90/NH<sub>4</sub>OH:MeOH:CHCl<sub>3</sub> to give 320 mg of a yellowish oil (1.02 mmol; quantitative). It could be crystallized from a highly concentrated solution in MeOH.

EXAMPLE 398-Methoxy-9-methyl-6-(1-piperazinyl)purine

To 125 mg of 6-[1-(4-BOC)piperazinyl]-8-methoxy-9-methylpurine (0.36 mmol) was added ca. 0.5 ml of trifluoroacetic acid. After the initial foaming subsided the solution was allowed to stand 15 minutes, then was evaporated under an N<sub>2</sub> stream to a thick gum. After repeated dissolution in about 1 ml of MeOH and re-evaporation, the crude product was dried under high vacuum for 15 min. The crude deblocked purine was taken up in ca. 0.5 ml of deionized water and carefully applied to a column of Dowex 1x2(OH) resin (5 ml). Collection of the eluant was begun and 20 ml of deionized water was run through. The eluate was lyophilized to give 105 mg (quantitative recovery) of a yellowish gum of the title compound as the free base.

EXAMPLE 406-[1-(4-BOC)piperazinyl]-9-methyl-8-(1-pyrrolidinyl)purine

A glass bomb liner was charged with 0.4 g 6-[1-(4-BOC)piperazinyl]-8-bromo-9-methylpurine (1.01 mmol), 30 ml of MeOH, and 10 ml of pyrrolidine, sealed, and heated at 130 °C with gentle agitation for 15 hours. The recovered material, after concentration to an oil under a N<sub>2</sub> stream, was purified on four 20x20cmx1000 μ silica GF plates developed with 3.30:70/NH<sub>4</sub>OH:MeOH:CHCl<sub>3</sub> to give 327 mg (0.84 mmol; 83% crude yield) of the title compound. Recrystallization from EtOH gave 146 mg pure product.

EXAMPLE 416-[1-(4-BOC)piperazinyl]-9-methyl-8-methylthiopurine

A mixture of 0.4 g 6-[1-(4-BOC)piperazinyl]-8-bromo-9-methylpurine (1.01 mmol), 500 mg thiourea (6.6 mmol), and 5.0 ml MeOH was refluxed for 30 hours. The resultant suspension was cooled to ambient temperature and 1.4 ml of 4M NaOMe in MeOH (5.6 mmol) was added with stirring; a clear solution resulted. To this was added 0.4 ml of CH<sub>3</sub>I (0.91 g; 6.4 mmol) and stirring was continued overnight under a N<sub>2</sub> atmosphere. The clear solution obtained was evaporated to a paste under a stream of N<sub>2</sub>, and the residue was taken up in a mixture of NaHCO<sub>3</sub>/H<sub>2</sub>O/CHCl<sub>3</sub>. The aq. phase was further extracted with CHCl<sub>3</sub>, the extracts combined, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give a thick yellowish oil. This was separated on silica gel, developed in acetone: CH<sub>2</sub>Cl<sub>2</sub> (1:4) to give the title compound.

EXAMPLE 429-Methyl-6-(1-piperazinyl)-8-(1-pyrrolidinyl)purine dihydrochloride

To 130 mg of 6-[1-(4-BOC)piperazinyl]-9-methyl-8-(1-pyrrolidinyl)purine (0.33 mmol) was added ca. 0.5 ml concentrated HCl. After 15 minutes, the solution was evaporated to a solid under a stream of N<sub>2</sub>. The residue was taken up in absolute EtOH with heating and the EtOH boiled off to azeotropically dry the product. The process was repeated a second time. The third time, the solution was concentrated and then diluted to 1.0 ml with absolute EtOH. After standing overnight, the crystals were isolated by filtration, washed with EtOH, EtOH/ether, and ether, then dried under N<sub>2</sub> to give 78 mg (0.29 mmol; 88% yield) of the title compound as a white powder.

Calculated for C<sub>14</sub>H<sub>21</sub>N<sub>7</sub>•2.1HCl•0.5 H<sub>2</sub>O

C, 45.08; H, 6.52; N, 26.29; Cl, 19.96.

Found:

C, 44.95; H, 6.12; N, 26.23; Cl, 19.91.

EXAMPLE 438-Dimethylamino-9-methyl-6-(1-piperazinyl)purine dihydrochloride

By substituting the appropriate 8-dimethylamino analog (see Example 38) in the reaction described above, (Example 42) the corresponding (title) product was obtained.

Calculated for C<sub>12</sub>H<sub>19</sub>N<sub>7</sub>•2.15HCl•0.6H<sub>2</sub>O

C, 41.12; H, 6.43; N, 27.98; Cl, 21.75.

Found:

C, 41.23; H, 6.16; N, 27.86; Cl, 21.90.

EXAMPLE 445-Amino-4-[1-(4-BOC)piperazinyl]-2-methyl-6-methylaminopyrimidine

5-Amino-4-chloro-2-methyl-6-methylaminopyrimidine (1.50 g; 8.7 mmol) and BOC-piperazine (7.50 g; 40.3 mmol) were mixed and heated at 130 °C in a melt. After 24 hrs, an additional 1.0 g of BOC-piperazine was added, and after 48 hrs, a further 2.0 g were added. The reaction was worked up after 55 hrs. total reaction time. The reaction mixture was dissolved in a minimum amount of CH<sub>2</sub>Cl<sub>2</sub> and absorbed onto a small amount of silica gel 60 by evaporation to dryness. This was placed atop a silica gel column (250 g) which was developed with EtOAc. Fractions containing the required product were pooled and evaporated to dryness to give 17 g of material contaminated with both starting materials. Further chromatography on another column of silica gel 60 (170 g), followed by preparative thick layer plates gave the title compound as a thick syrup (500 mg; 18% yield) contaminated with a trace amount of BOC-piperazine.

EXAMPLE 45

6-[1-(4-BOC)piperazinyl]-2,8,9-trimethylpurine

To the foregoing material prepared in Example 44, (490 mg; 1.6 mmol) in 2-methoxyethanol (2.5 ml) was added acetamidine acetate (378 mg; 3.2 mmol) and the mixture was heated under reflux for 20 hr. Upon cooling, 10% aq. Na<sub>2</sub>CO<sub>3</sub> was added and the mixture was extracted with EtOAc. The pooled organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated to dryness. This residue was chromatographed on a column of silica gel 60 (100 g) developed in EtOAc and then a step gradient of MeOH in EtOAc (upto 10% MeOH) to give 340 mg of the title compound (61%) which was slightly contaminated by NMR evaluation. Crystallization from cyclohexane gave material suitable for deblocking.

EXAMPLE 466-(1-Piperazinyl)-2,8,9-trimethylpurine dihydrochloride

The foregoing material prepared in Example 45, (97 mg; 0.28 mmol) was dissolved in absolute EtOH (3 ml) and ethanolic HCl (2 ml) was added. This solution was allowed to stand at room temperature for 1 hour and then was blown down to dryness under a stream of nitrogen. Trituration under Et<sub>2</sub>O containing a little EtOH gave 79 mg of crude material which contained some impurities. This was recrystallized from abs. EtOH to give 22 mg of impure material, but the mother liquors, after concentration to dryness gave 49 mg of analytically pure product. Mass spectrum showed molecular ion m/e = 246.

Calculated for C<sub>12</sub>H<sub>18</sub>N<sub>6</sub>•2HCl•1.2 H<sub>2</sub>O:

C, 42.28; H, 6.62; N, 24.42.

Found:

C, 42.11; H, 6.46; N, 24.66.

EXAMPLE 474-[1-(4-BOC)piperazinyl]-5,6-diamino-2-methylpyrimidine

This was prepared in a manner similar to that described in Example 10 for 4-[1-(4-BOC)piperazinyl]-5,6-diaminopyrimidine except that 6-chloro-4,5-diamino-2-methylpyrimidine was used as the starting material. The title compound was obtained in a yield of 74% after silica gel chromatography.

EXAMPLE 486-[1-(4-BOC)piperazinyl]-2,8-dimethylpurine

The foregoing material prepared in Example 47, (450 mg; 1.46 mmol) was dissolved in 2-methoxyethanol (5ml) and acetamidine acetate (354 mg; 3 mmol) was added. This solution was heated at reflux for 24 hrs, when tlc indicated completion of the reaction. The mixture was cooled to room temperature and 10% aq. Na<sub>2</sub>CO<sub>3</sub> was added, followed by EtOAc. The required product was insoluble and was filtered off and washed with H<sub>2</sub>O and then EtOAc, to give 258 mg of the title compound (0.78 mmol, 53% yield).

Calculated for C<sub>16</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>•0.6H<sub>2</sub>O:

C, 55.98; H, 7.40; N, 24.49.

Found:

C, 55.61; H, 7.09; N, 24.16.

EXAMPLE 492,8-Dimethyl-6-1(1-piperaziny)purine hydrochloride

The foregoing material (113 mg, 0.34 mmol) was dissolved in hot EtOH (8 ml) and ethanolic HCl (4 ml) was added. After 1 hour at room temperature, the solution was blown down to dryness under a stream of nitrogen and the residue was triturated under EtOH:Et<sub>2</sub>O (1:1, 4 ml). The solid so obtained was washed with Et<sub>2</sub>O and dried to give 107 mg of the title compound. This was recrystallized from EtOH to give 66 mg of product (0.21 mmol, 62%)

Calculated for C<sub>11</sub>H<sub>15</sub>N<sub>5</sub>•2HCl•0.4 H<sub>2</sub>O:

C, 42.28; H, 6.06; N, 26.90.

Found:

C, 42.48; H, 5.45; N, 26.48.

EXAMPLE 506-[1-(4-BOC)piperaziny]-2-chloropurine

A solution of 2,6-dichloropurine (10.02 g, 52.0 mmol), BOC-piperazine (11.85 g; 63.6 mmol) and triethylamine (11.08 ml; 79.5 mmol) in absolute EtOH (200 ml) was allowed to stir at room temperature for 40 min. (white precipitate formed) and then was heated at 70-80 °C (bath-temp) under a reflux condenser, under nitrogen for 3 hours. The mixture was cooled and the precipitate which formed was collected by filtration. Yield 16.27 g (48.02 mmol, 90.6%).

Calculated for C<sub>14</sub>H<sub>19</sub>N<sub>5</sub>ClO<sub>2</sub>:

C, 49.63; H, 5.65; N, 24.81.

Found:

C, 49.60; H, 5.69; N, 24.49.

EXAMPLE 516-[1-(4-BOC)piperaziny]-2-chloro-9-methylpurine

6-[1-(4-BOC)piperaziny]-2-chloropurine (5.76 g, 17.0 mmol) was dissolved in sieve-dried DMF (100 ml) and anhydrous K<sub>2</sub>CO<sub>3</sub> (2.58 g, 18.7 mmol) and methyl iodide (2.12 ml, 34.0 mmol) were added. This mixture was stirred overnight at room temperature, under a Drierite guard tube. The mixture was evaporated to dryness in vacuo and the residue was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. Some solid remained undissolved and this was filtered off and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The total organic layers were pooled and evaporated to dryness to give a white solid residue which was triturated under Et<sub>2</sub>O and filtered. The solid was air-dried to give 4.14 g of the title compound (69% yield).

Calculated for C<sub>15</sub>H<sub>21</sub>N<sub>5</sub>ClO<sub>2</sub>•3H<sub>2</sub>O:

C, 50.29; H, 6.08; N, 23.46.

Found:

C, 50.58; H, 5.90; N, 23.25.

EXAMPLE 52

2-Chloro-9-methyl-6-(1-piperaziny)purine hydrochloride

The foregoing material prepared in Example 51, (247 mg, 0.70 mmol) was dissolved in absolute EtOH (8 ml) and to this solution was added EtOH saturated with HCl (3 ml). A solid precipitated immediately and was removed by centrifugation after concentration of the mixture to 4 ml under a stream of nitrogen. Thin layer chromatography of this solid indicated incomplete deblocking and it was treated again with ethanolic HCl for 3 hours. The solid was recovered by filtration, washed with EtOH, and dried to give 124 mg (0.43 mmol; 61% yield) of the title compound.

Calculated for  $C_{10}H_3N_6Cl \cdot HCl \cdot 0.4H_2O$ :

C, 40.53; H, 5.03; N, 28.36; Cl, 23.92.

Found:

C, 41.18; H, 4.88; N, 27.81; Cl, 23.78.

EXAMPLE 536-[1-(4-BOC)piperaziny]-9-methyl-2-morpholinopurine

6-[1-(4-BOC)piperaziny]-2-chloro-9-methylpurine (352.8 mg, 1.0 mmol) was dissolved in distilled morpholine (5 ml) and heated (bath-temp. 150 °C) under  $N_2$  for 27 hours. The reaction mixture was cooled to room temperature and then evaporated to dryness in vacuo (several times from toluene to remove the last traces of morpholine). The residue was dissolved in a minimum amount of  $CH_2Cl_2$  and absorbed onto silica gel 60. This was placed on top of a silica gel 60 column (40 g) packed in hexanes. The column was developed successively with EtOAc: hexanes (2:3), EtOAc:hexanes (1:1), and finally with EtOAc:hexanes (3:2). Fractions containing the required product were pooled and evaporated to dryness to give 368 mg (91% yield) of the title compound.

Calculated for  $C_{19}H_{29}N_7O_3 \cdot 0.35H_2O$ :

C, 55.64; H, 7.29; N, 23.91.

Found:

C, 55.92; H, 6.84; N, 23.52.

EXAMPLE 549-Methyl-2-morpholino-6-(1-piperaziny)purine dihydrochloride

The foregoing material prepared in Example 63, (310 mg; 0.77 mmol) was dissolved in absolute EtOH (7 ml) and EtOAc (2 ml), with warning. To this solution was added EtOH saturated with HCl (4 ml) and the mixture was left at room temperature for 1 hour. The mixture was concentrated to 5 ml under a stream of nitrogen and  $Et_2O$  (5 ml) was added. The solid so formed was isolated by centrifugation and washed 3 times with  $Et_2O$  to give the title compound in good yield.

Calculated for  $C_{14}H_{21}N_7O \cdot 2HCl$ :

C, 44.68; H, 6.16; N, 26.06.

Found:

C, 44.75; H, 6.39; N, 25.75.

EXAMPLE 55



6-[1-(4-BOC)piperazinyl]-9-methyl-2-pyrrolidinylpurine

6-[1-(4-BOC)piperazinyl]-2-chloro-9-methylpurine (0.396 g; 1.12 mmol) was dissolved in EtOH (15 ml) and pyrrolidine (10 ml) was added. This solution was heated under reflux (bath temp 120-130 °C) for 6 hours and allowed to cool to room temperature. The mixture was evaporated to dryness and the residue was separated between CH<sub>2</sub>Cl<sub>2</sub> (70 ml) and 10% aq. Na<sub>2</sub>CO<sub>3</sub> (70 ml). The aq. layer was washed two more times with CH<sub>2</sub>Cl<sub>2</sub> (2x70ml) and the pooled organic layers were dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness in vacuo to give 0.450 g (quantitative yield) of the title compound as a white powder.

Calculated for C<sub>19</sub>H<sub>29</sub>N<sub>7</sub>O<sub>2</sub>•0.3H<sub>2</sub>O:

C, 58.08, H, 7.65, N, 24.96.

Found:

C, 58.35; H, 7.56; N, 24.69.

EXAMPLE 569-Methyl-6-(1 piperazinyl)-2-pyrrolidinylpurine dihydrochloride

The foregoing material prepared in Example 55, (0.410 g; 1.06 mmol) was dissolved in EtOAc (30 ml) and ethanolic HCl (15 ml) was added. After standing at room temperature for 1 1/2 hour, the solution was blown down under a stream of nitrogen to a syrup. This was triturated under EtOH-Et<sub>2</sub>O (8 ml) to give a white powder which was washed with Et<sub>2</sub>O and dried in vacuo to give 315.3 mg (0.87 mmol; 83%) of the title compound.

Calculated for C<sub>14</sub>H<sub>21</sub>N<sub>7</sub>•2HCl•0.25H<sub>2</sub>O

C, 46.10; H, 6.49; N, 26.88.

Found:

C, 46.11; H, 6.32; N, 26.55.

EXAMPLE 576-[1-(4-BOC)piperazinyl]-9-methyl-2-methylaminopurine

A suspension of 6-[1-(4-BOC)piperazinyl]-2-chloro-9-methylpurine (0.250 g; 0.71 mmol) in EtOH (6 ml) was cooled to 0 ° and added to anhydrous methylamine (3 ml) condensed in a pressure table. The tube was sealed and scaled at 110 ° C for 5 1/2 hours. After cooling to room temperature, CH<sub>2</sub>Cl<sub>2</sub> and 10% aq. Na<sub>2</sub>CO<sub>3</sub> were added and the layers were separated. The aqueous layer was washed two more times with CH<sub>2</sub>Cl<sub>2</sub> and the pooled organic layers were dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. The residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> (5ml)-hexanes (20 ml) to give 150 mg (0.45 mmol, 63%) of the title compound in two crops.

Calculated for C<sub>16</sub>H<sub>25</sub>N<sub>7</sub>O<sub>2</sub>:

C, 55.31; H, 7.25; N, 28.22.

Found:

C, 55.46; H, 7.22; N, 28.31.

EXAMPLE 58

9-Methyl-2-methylamino-6-(1-piperazinyl)purine dihydrochloride

This was prepared from the foregoing compound prepared in Example 57 by deblocking with ethanolic HCl in the usual fashion.

- 5 Calculated for  $C_{11}H_{17}N_7 \bullet HCl$ :  
 C, 41.26; H, 5.98; N, 30.62.  
 Found:  
 C, 41.07; H, 6.05; N, 30.29.

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EXAMPLE 59

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6-[1-(4-BOC)piperazinyl]-2-dimethylamino-9-methylpurine20 Method A

- 6-[1-(4-BOC)piperazinyl]-2-chloro-9-methylpurine (0.49 g; 1.41 mmol) was dissolved in EtOH (15 ml), chilled, and added to 10 ml of anhydrous dimethylamine (condensed at  $-78^{\circ}C$ ) in a Fischer-Porter tube. The tube was sealed and heated at  $120-130^{\circ}$  for 5 hours. After cooling to room temperature, the reaction  
 25 mixture was evaporated to dryness to give a white residue of 0.58 g. This was separated between  $CH_2Cl_2$  - (70 ml) and 10% aq.  $Na_2CO_3$  (70 ml) and the aqueous layer was washed two more times with  $CH_2Cl_2$  (2x70 ml). The pooled organic layers were dried ( $MgSO_4$ ), filtered, and evaporated to dryness to give 0.50 g (1.38 mmol, 98%) of the title compound.

- Calculated for:  $C_{17}H_{27}N_7O_2$ :  
 30 C, 56.49; H, 7.53; N, 27.13.  
 Found:  
 C, 56.65; H, 7.58; N, 26.95.

35 Method B

- 6-[1-(4-BOC)piperazinyl]-2-chloro-9-methylpurine (0.352 g; 1.0 mmol) was dissolved in n-butanol (30 ml) and 40% aq. dimethylamine (10 ml) was added. This mixture was heated in a sealed tube at  $150^{\circ}C$  for 24 hours, at which point tlc indicated no starting material remaining, but two products were apparent. The  
 40 reaction mixture was blown down under a stream of nitrogen and then was evaporated to dryness. This residue was absorbed onto silica gel 60 from a methanolic solution, and then was fractionated on a silica gel 60 column (30 g). The column was developed first with EtOAc:hexanes (1:1) to give 110 mg (30% yield) of the title compound identical by tlc and NMR with that prepared by Method A (above).

- Calculated for:  $C_{17}H_{27}N_7O_2$ :  
 45 C, 56.49; H, 7.53; N, 27.13  
 Found:  
 C, 56.83; H, 7.65; N, 26.99

Further development of the column with  $CH_2Cl_2$ : MeOH 9:1 gave 180 mg (69% yield) of 2-dimethylamino-9-methyl-6-(1-piperazinyl)purine as the free base.

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EXAMPLE 60

55

2-Dimethylamino-9-methyl-6-(1-piperazinyl)purine dihydrochloride

Method A

The free base of the title compound obtained by Method B in the foregoing example (Example 59) (165 mg; 0.63 mmol) was dissolved in EtOH (4 ml) and ethanolic HCl (2 ml) was added. The solution was blown down under a stream of nitrogen and the residue was triturated under EtOH (2 ml). A solid formed which was washed with EtOH (0.5 ml) and then Et<sub>2</sub>O before being dried in vacuo overnight at 40 °C to give 96 mg (0.27 mmol) of the title compound.

Calculated for C<sub>12</sub>H<sub>13</sub>N<sub>7</sub>•2HCl•1.3H<sub>2</sub>O:

C, 40.30; H, 6.64; N, 27.42.

Found:

C, 40.34; H, 6.30; N, 27.06.

Method B

6-[1-(4-BOC)piperazinyl]-2-dimethylamino-9-methylpurine (50 mg; 0.14 mmol) was dissolved in EtOH (4 ml) and ethanolic HCl (2 ml) was added. After 1 hour at room temperature, the solution was blown down to about 1 ml under a stream of nitrogen. Product precipitated and an additional 2 ml of Et<sub>2</sub>O was added. The solid was washed by centrifugation with Et<sub>2</sub>O (2x2 ml) and dried at 40 °C in vacuo to give 42 mg (0.13 mmol, 93%) of the title compound identical in all respects to that prepared by Method A (above).

EXAMPLE 616-[1-(4-BOC)piperazinyl]-8-bromo-2-dimethylamino-9-methylpurine

6-[1-(4-BOC)piperazinyl]-2-dimethylamino-9-methylpurine (0.48 g; 1.33 mmol) was dissolved in dioxane (25 ml), with warming, and a solution of K<sub>2</sub>HPO<sub>4</sub> 2.39 g) in H<sub>2</sub>O (25 ml) was added. To this well-stirred solution was added bromine (0.2 ml), dropwise over a period of 1-2 min. After 45 min. at room temperature, the reaction was blown under a stream of nitrogen and evaporated to dryness. The residue so obtained was separated between CH<sub>2</sub>Cl<sub>2</sub> (60 ml) and 10% aq. Na<sub>2</sub>CO<sub>3</sub> (60 ml), and the aqueous layer was washed two more times with 60 ml of CH<sub>2</sub>Cl<sub>2</sub>. The pooled organic layers were dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness to give 0.44 g. This residue was purified by chromatography on silica gel 60 using CH<sub>2</sub>Cl<sub>2</sub> and a step gradient of EtOH in CH<sub>2</sub>Cl<sub>2</sub> as developing solvents, and then rechromatography using EtOAc-hexanes, gave 198.2 mg of the title compound in 34% yield.

Calculated for C<sub>17</sub>H<sub>26</sub>N<sub>7</sub>O<sub>2</sub>Br:

C, 46.37; H, 5.95; N, 22.27.

Found:

C, 46.57; H, 5.98; N, 22.08.

EXAMPLE 626-[1-(4-BOC)piperazinyl]-2,8-bis(dimethylamino)-9-methylpurine

The foregoing material prepared in Example 61, (198.2 mg; 0.45 mmol) was dissolved in n-butanol (10 ml), with warming, and added to anhydrous dimethylamine (10 ml) (condensed at -78 °C) in a pressure bottle. This solution was sealed and heated at 120-130 °C for 4 hours. TLC indicated the reaction to be incomplete, and an additional 10 ml of condensed dimethylamine was added and the reaction continued overnight. The mixture was then cooled to room temperature, blown down to small volume under a stream of nitrogen, and evaporated to dryness. This residue was separated between CH<sub>2</sub>Cl<sub>2</sub> (60 ml) and 10% aq. Na<sub>2</sub>CO<sub>3</sub> (60 ml) and the aqueous layer was washed two more times (2x 60 ml) with CH<sub>2</sub>Cl<sub>2</sub>. The pooled

organic layers were dried ( $\text{MgSO}_4$ ), filtered, and evaporated to dryness. This residue was chromatographed on a column (2x36 cm) of silica gel 60 developed successively with a step gradient of EtOAc in hexanes (10% increments starting with EtOAc:hexanes 1:9). Fractions containing the required product were pooled and evaporated to dryness to give a quantitative yield of the title compound as a clear glass which solidified on standing overnight.

Calculated for  $\text{C}_{19}\text{H}_{32}\text{N}_8\text{O}_2 \cdot 0.25\text{H}_2\text{O}$ :

C, 55.79; H, 8.01; N, 27.40.

Found:

C, 55.91; H, 7.65; N, 27.31.

### EXAMPLE 63

#### 2,8-Bis(dimethylamino)-9-methylpurine dihydrochloride

The foregoing material (180 mg; 0.44 mmol) was dissolved in EtOH (5 ml) and ethanolic HCl (5 ml) was added. After standing at room temperature for 15 minutes, the solution was slowly blown down to a syrup under a stream of nitrogen. This residue was triturated under EtOH-Et<sub>2</sub>O (8 ml) and the solid so formed was isolated and washed with Et<sub>2</sub>O to give 121.3 mg (0.32 mmol; 73%) of the title compound. An analytical sample was obtained by reconversion to the free base (extraction into  $\text{CH}_2\text{Cl}_2$  from 10% aq.  $\text{Na}_2\text{CO}_3$ ), followed by re-conversion to the dihydrochloride salt by treatment with ethanolic HCl.

Calculated for  $\text{C}_{14}\text{H}_{24}\text{N}_8 \cdot 2\text{HCl} \cdot 0.4\text{H}_2\text{O}$ :

C, 43.73; H, 7.03; N, 29.14.

Found:

C, 43.95; H, 6.95; N, 28.83.

### EXAMPLE 64

#### 6-[1-(4-BOC)piperazinyl]-2-methoxy-9-methylpurine

Sodium spheres (110 mg, 4.8 mmol) were dissolved in anhydrous methanol (10 ml) and 6-[1-(4-BOC)-piperazinyl]-2-chloro-9-methylpurine (430 mg, 1.2 mmol) was added. This mixture was heated under reflux under nitrogen for 4 days and then allowed to cool to room temperature. The reaction was neutralized with glacial acetic acid and evaporated to dryness in vacuo to give a white residue. This was adsorbed onto silica gel 60 and placed on top of a silica gel 60 column (90 ml), packed in hexanes. The column was developed successively with EtOAc:hexanes (1:4), EtOAc:hexanes (3:7), EtOAc:hexanes (1:1) and finally, EtOAc:hexanes (3:2). Fractions containing the required product were pooled and evaporated to dryness to give a residue which was triturated under hexanes to give a 64% yield of the title compound as a white solid.

Calculated for  $\text{C}_{16}\text{H}_{24}\text{N}_6\text{O}_3$ :

C, 55.16; H, 6.94; N, 27.12.

Found:

C, 55.34; H, 6.84; N, 24.06.

### EXAMPLE 65

2-Methoxy-9-methyl-6-(1-piperaziny)purine dihydrochloride

The foregoing compound prepared in Example 64, (2.1 mg, 0.6 mmol) was dissolved in absolute EtOH (5 ml) with warming. To this solution was added EtOH saturated with HCl (2 ml) and after 1 hour the solution was concentrated to 4 ml under a stream of nitrogen. The white precipitate so formed was collected by centrifugation and washed with Et<sub>2</sub>O (4x2 ml). Re-working of the supernatants gave 51 mg (0.16 mmol; 26%) in total, of the title compound, m.p. >280 °C.

Calculated for C<sub>11</sub>H<sub>16</sub>N<sub>6</sub>O•2HCl•1.25H<sub>2</sub>O:

C, 38.44; H, 6.01; N, 24.45.

Found:

C, 38.44; H, 5.88; N, 26.16.

EXAMPLE 666-[1-(4-BOC)piperaziny]-9-methyl-2-(2-propoxy)purine

Sodium spheres (92 mg, 4 mmol) were dissolved in 2-propanol (9 ml) and 6-[1-(4-BOC)piperaziny]-2-chloro-9-methylpurine (352.8 mg; 1 mmol) was added. This mixture was heated under reflux under nitrogen for 3 days and then was evaporated to dryness in vacuo. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O and the organic layer was dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness. This residue was adsorbed onto silica gel 60 and placed on top of a silica gel 60 column (50 g), packed in hexanes. The column was developed successively with EtOAc:hexanes (1:3), EtOAc:hexanes (1:1), and finally with EtOAc:hexanes (3:2). Fractions containing the required product were pooled and evaporated to dryness to give 214 mg of the title compound (57% yield).

Calculated for C<sub>28</sub>H<sub>38</sub>N<sub>6</sub>O<sub>3</sub>•0.25 H<sub>2</sub>O:

C, 56.75; H, 7.54; N, 22.06.

Found:

C, 56.73; H, 7.35; N, 21.66.

EXAMPLE 679-Methyl-6-(1-piperaziny)-2-(2-propoxy)purine dihydrochloride

The foregoing material prepared in Example 66, (204 mg, 0.54 mmol) was dissolved in absolute EtOH (5 ml) and to this solution was added ethanolic HCl (3 ml). After 1 hour at room temperature, this solution was concentrated to 4 ml under a stream of nitrogen. Ether (4 ml) was added and the white solid so formed was isolated by centrifugation and washed well (3x) with ether. Yield 132 mg (2 crops), 71% yield.

Calculated for C<sub>13</sub>H<sub>20</sub>N<sub>6</sub>O•2HCl•1.15 H<sub>2</sub>O:

C, 42.20; H, 6.60; N, 22.72.

Found:

C, 41.97; H, 6.18; N, 22.61.

EXAMPLE 68

6-[1-(4-BOC)piperazinyl]-2-dimethylaminopurine

A suspension of 6-[1-(4-BOC)piperazinyl]-2-chloropurine (0.25 g; 0.74 mmol) in EtOH (6 ml) was cooled to 0° and added to anhydrous dimethylamine (3 ml) condensed in a pressure bottle. The bottle was sealed and heated at 110° C for 5 1/2 hr. The mixture became homogeneous as the reaction progressed. At completion of the reaction, the tube was cooled and the mixture was blown down under a stream of nitrogen. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aq. Na<sub>2</sub>CO<sub>3</sub> and the organic phase was dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness. Further separation between CH<sub>2</sub>Cl<sub>2</sub> and 10% aq. Na<sub>2</sub>CO<sub>3</sub>, followed by re-working of the organic phase as described above, gave the title compound in 97% yield (250 mg; 0.71 mmol).

Calculated for C<sub>16</sub>H<sub>25</sub>N<sub>7</sub>O<sub>2</sub>:  
C, 55.31; H, 7.25; N, 28.22.  
Found:  
C, 54.95; H, 7.25; N, 28.51.

EXAMPLE 692-Dimethylamino-6-(1-piperazinyl)purine dihydrochloride

The foregoing material prepared in Example 68, (220 mg; 0.63 mmol) was dissolved in hot EtOH (20 ml) and cooled to room temperature. Ethanolic HCl (10 ml) was added and the mixture was allowed to stand at room temperature for 1 hour (product started to precipitate after about 30 min.). The mixture was then blown down to about 10 ml under a stream of nitrogen and then Et<sub>2</sub>O (10 ml) was added. The precipitated product was filtered off and washed with Et<sub>2</sub>O. Yield 0.218 g (quantitative yield)

Calculated for C<sub>11</sub>H<sub>17</sub>N<sub>7</sub>•2HCl•2.8 H<sub>2</sub>O  
C, 35.64; H, 6.40; N, 26.45.  
Found:  
C, 35.39; H, 6.02; N, 26.30.

EXAMPLE 702-Chloro-6-[1-(4-methylpiperazinyl)]purine

2,6-Dichloropurine (4.53 g; 24 mmol) was dissolved in EtOH (100 ml) and N-methylpiperazine (2.90 g, 29 mmol) was added, followed by triethyl amine (5.01 ml, 36 mmol). This mixture was heated under reflux for 45 min. (tlc after 15 min showed traces of starting material). Upon cooling to room temperature, the product precipitated and was filtered off and dried. Yield 5.80 g (23 mmol, 96%)

Calculated for C<sub>10</sub>H<sub>17</sub>N<sub>6</sub>Cl:  
C, 47.53; H, 5.18; N, 33.26.  
Found:  
C, 47.43; H, 5.34; N, 33.03.

EXAMPLE 71

2-Dimethylamino-6-[1-(4-methylpiperazinyl)]purine dihydrochloride

The foregoing material prepared in Example 70, (0.700 g; 2.77 mmol) was added to anhydrous dimethylamine (5 ml; condensed in a pressure tube) and chilled EtOH (8 ml) was added. The tube was sealed and heated at 110° C for 5 1/2 hours, during which time dissolution occurred. Upon cooling to room temperature a solid formed and the cooled mixture was blown down to dryness under a stream of nitrogen. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and extracted with 10% aq. Na<sub>2</sub>CO<sub>3</sub> and the organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness to give 0.650 g (2.49 mmol; 90% yield) of the title compound as the free base. A portion, 0.100 g (0.38 mmol), of this material was dissolved in hot EtOH (8 ml) and cooled to room temperature. Ethanolic HCl (4 ml) was added and the product started to precipitate out after ca. 5 min. After 1 hour, the solution was blown down under a stream of nitrogen and the residue was triturated under EtOH-Et<sub>2</sub>O. The precipitated product was filtered and washed with Et<sub>2</sub>O. Yield 0.122 g (0.37 mmol; 97% from free base).

Calculated for C<sub>12</sub>H<sub>19</sub>N<sub>7</sub>•2HCl•2.4 H<sub>2</sub>O:

C, 38.17; H, 6.88; N, 25.97.

Found.

C, 37.89; H, 6.45; N, 25.76.

EXAMPLE 722-Dimethylamino-9-methyl-6-[1-(4-methylpiperazinyl)]purine dihydrochloride

The free base of the foregoing material prepared in Example 71, (150 mg; 0.58 mmol) was dissolved in sieve-dried DMF (10 ml) and NaH (60% in oil; 40 mg, 24 mg of NaH, 1 mmol) was added. This mixture was stirred at room temperature under N<sub>2</sub> until evolution of hydrogen gas had ceased (20 min). Methyl iodide (0.043 ml; 0.7 mmol) was then added and the mixture was stirred at room temperature for 3 1/2 hr. The mixture was then evaporated to dryness in vacuo and the residue was adsorbed onto a minimum amount of silica gel 60 by evaporation of a methanolic solution. This was placed atop a silica gel 60 column (20 g) packed in CH<sub>2</sub>Cl<sub>2</sub> which was developed successively with MeOH:CH<sub>2</sub>Cl<sub>2</sub> 5:95 and then MeOH:CH<sub>2</sub>Cl<sub>2</sub> 1:9. Fractions containing the required product were pooled and evaporated to dryness to give 163mg (quantitative yield) of the title compound as the free base.

0.115 g (0.42 mmol) of this material was dissolved in hot EtOH (8 ml) and cooled to room temperature. Ethanolic HCl (4 ml) was added and after 30 min at room temperature the mixture was blown down to dryness under a stream of nitrogen. Trituration under EtOH-Et<sub>2</sub>O gave the title compound which was filtered off and washed with Et<sub>2</sub>O. After drying, 85 mg (0.24 mmol, 57%) was obtained.

Calculated for C<sub>13</sub>H<sub>21</sub>N<sub>7</sub>•2HCl•H<sub>2</sub>O

C, 42.62; H, 6.88; N, 26.77.

Found:

C, 42.9; H, 6.73; N, 26.43.

EXAMPLE 732-Amino-6-(1-piperazinyl)purine dihydrochloride

2-Amino-6-chloropurine (508 mg, 3.00 mmol) was suspended in sieve-dried DMF (20 ml) and piperazine (516 mg; 5.99 mmol) was added. Dissolution occurred and the mixture was heated at 100° C overnight under nitrogen. A precipitate formed which was filtered off and washed with Et<sub>2</sub>O (yield, 380 mg). A portion (50 mg) was dissolved in 2N HCl (1 ml) and centrifuged, the supernatant was removed and cooled in an ice-bath and the crystalline product (40 mg) was isolated by centrifugation and dried in vacuo at 70° C for 12 hours over P<sub>2</sub>O<sub>5</sub>.

Calculated for  $C_9H_{13}N_7 \cdot 2HCl \cdot 0.69 H_2O$ :

C, 35.49; H, 5.42; N, 32.20; Cl, 23.28.

Found:

C, 35.74; H, 5.36; N, 31.97; Cl, 23.20.

5

#### EXAMPLE 74

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#### 6-[1-(4-BOC)piperazinyl]-2-chloro-9-(1-propyl)purine

The material prepared in Example 50 (3.73 g, 11.0 mmol) was dissolved in sieve dried DMF (100 ml) and 60% NaH in oil (660 mg, 16.5 mmol of NaH) was added and the mixture was stirred under nitrogen until the effervescence ceased. 1-Iodopropane (1.23 ml, 12.65 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was evaporated to dryness in vacuo and the residue was dissolved in  $CH_2Cl_2$  and this solution was washed with 10% aq.  $Na_2CO_3$ , dried over  $MgSO_4$ , filtered and evaporated to a yellow oil. This was dissolved in a little  $CH_2Cl_2$  and chromatographed on a silica gel 60 column (200 ml) packed in EtOAc : hexanes (1 : 2). The column was developed successively with EtOAc : hexanes (1 : 2) and EtOAc : hexanes (1 : 1) and fractions containing the required product were pooled and evaporated to dryness to give a syrup which crystallized upon trituration. These white crystals were triturated under hexane and filtered. Yield 2.85 g (74.8 mmol, 68%). Mp 105-106.5 °C.

Calculated for  $C_{17}H_{25}N_6O_2Cl$ :

C, 53.61; H, 6.62; N, 22.06

Found:

C, 53.39; H, 6.47; N, 22.06

30

#### EXAMPLE 75

#### 6-[1-(4-BOC)piperazinyl]-2-methoxy-9-(1-propyl)purine

The foregoing material prepared in Example 74 (72.52 g, 0.17 mol) was dissolved in methanol (1.06 L) and 122 ml of 4.38 M methanolic sodium methoxide was added. This solution was heated under reflux under  $N_2$  for 48 hrs. and then additional sodium methoxide (12 ml) was added, followed by another 6 ml after a further 24 hrs. After 96 hrs total reaction, the mixture was evaporated to dryness and the residue was partitioned between  $CH_2Cl_2$  (1L) and  $H_2O$  (400 ml). The aqueous layer was washed with  $CH_2Cl_2$  (2 x 500 ml) and the pooled organic layers were dried ( $MgSO_4$ ), filtered and evaporated to dryness. Purification was effected on a silica gel 60 column (2.1 kg) developed with a step gradient (1 : 4 to 1 : 1) of EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 52 g (0.138 mol, 81%) of the title compound.

Calculated for  $C_{18}H_{28}N_6O_3$ :

C, 57.43; H, 7.50; N, 22.33

Found:

C, 57.58; H, 7.66; N, 22.33

50

#### EXAMPLE 76

55



2-Methoxy-6-(1-piperazinyl)-9-(1-propyl)purine dihydrochloride

The foregoing material prepared in Example 75 (51.5 g, 0.137 mol) was dissolved in MeOH (1.5 L) and 1.5L of methanolic HCl was added carefully. This mixture was stirred at room temperature for 1 1/2 hr. and then was concentrated first under a stream of N<sub>2</sub> and then on an evaporator to 600 ml. Precipitation occurred and Et<sub>2</sub>O (1L) was added. The white solid was filtered off and washed well with Et<sub>2</sub>O. Yield 39.4 g, and a second crop gave 3.54 g. Total yield 0.123 mol, 90%. Mp 205-207 °C

Calculated for C<sub>13</sub>H<sub>20</sub>N<sub>6</sub>O•2HCl:

C, 44.70; H, 6.35; N, 24.06; Cl, 20.30

Found:

C, 44.50; H, 6.50; N, 23.98; Cl, 20.64

EXAMPLE 776-[1-(4-BOC)piperazinyl]-2-methylthio-9-(1-propyl)purine

The material prepared in Example 74 (300 mg, 0.76 mmol) was dissolved in t-butanol (10 ml) and sodium methylthiolate (213 mg, 3.04 mmol) was added. This mixture was refluxed under N<sub>2</sub> for 48 hrs. and then volatiles were removed under a stream of N<sub>2</sub>. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (20 ml) and the layers were separated. The aqueous layer was washed two more times with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 ml) and the pooled organic layers were dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness. This residue was dissolved in a little EtOAc and passed onto a silica gel 60 column (20 g), packed and developed with EtOAc. Fractions containing the required product were pooled and evaporated to dryness to give 177 mg (0.45 mmol, 59%) of chromatographically pure product.

Calculated for C<sub>18</sub>H<sub>28</sub>N<sub>5</sub>O<sub>2</sub>S:

C, 55.08; H, 7.19; N, 21.41

Found:

C, 55.31; H, 7.18; N, 21.18

EXAMPLE 782-Methylthio-6-(1-piperazinyl)-9-(1-propyl)purine dihydrochloride

The foregoing material prepared in Example 77 (150 mg, 0.38 mmol) was dissolved in EtOH (7.5 ml) and ethanolic HCl (3.5 ml) was added. After standing at room temperature for 1 hr, the mixture was concentrated in 1 ml under a stream of N<sub>2</sub>. Precipitation of the product was completed by the addition of Et<sub>2</sub>O (4 ml) and the title compound was filtered and washed with Et<sub>2</sub>O (2 x 2 ml). Yield 126 mg (0.34 mmol, 89%).

Calculated for C<sub>13</sub>H<sub>20</sub>N<sub>6</sub>S•2HCl:

C, 42.74; H, 6.07; N, 23.01

Found:

C, 42.69; H, 6.06; N, 22.68

EXAMPLE 79

6-[1-(4-BOC)piperazinyl]-2-chloro-9-(methoxymethyl)purine

The material prepared in Example 50 (1.02 g, 3.0 mmol) was dissolved in sieve dried DMF (25 ml) and 60° NaH in oil (180 mg, 4.5 mmol of NaH) was added and the mixture was stirred under N<sub>2</sub>. When a homogeneous solution was obtained, bromomethyl methyl ether (0.27 ml, 3.3 mmol) was added and the mixture was left stirring at room temperature under N<sub>2</sub> overnight. Additional bromomethyl methyl ether (0.05 ml) was added followed, at hourly intervals, by two additional 24 mg amounts of 60% NaH in oil. Cold H<sub>2</sub>O (25 ml) was added slowly, followed by 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (10 ml). After stirring for 1 1/2 hr., the mixture was evaporated to dryness in vacuo and the residue was partitioned between 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated, filtered, and adsorbed onto a small amount of silica gel 60. This was placed atop a dry packed silica gel 60 column (80 ml) which was developed with a step gradient (from 1 : 4 to 1 : 1) of EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 927 mg (2.42 mmol, 80%) of an oil which crystallized on standing. Mp 108-110°.

Calculated for C<sub>15</sub>H<sub>23</sub>N<sub>6</sub>O<sub>3</sub>Cl:

15 C, 50.20; H, 6.06; N, 21.95

Found:

C, 50.28; H, 6.10; N, 22.05

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EXAMPLE 8025 6-[1-(4-BOC)piperazinyl]-2-ethoxy-9-methoxymethyl)purine

Sodium spheres (83 mg, 3.6 mmol) were added to abs. EtOH (5 ml) and after hydrogen evolution had ceased, 354 mg 0.92 mmol) of material from the foregoing Example 79 in 5 ml of EtOH was added. This solution was heated under reflux overnight under N<sub>2</sub>. The mixture was cooled and carefully neutralized with acetic acid before being evaporated to dryness. This residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and a little EtOAc was then added to the CH<sub>2</sub>Cl<sub>2</sub> layer to effect total dissolution. After drying (MgSO<sub>4</sub>) and filtration, the filtrate was evaporated to an oil (310 mg, 86%) which crystallized on standing. Trituration under Et<sub>2</sub>O and then evaporation of the mixture gave 257 mg (0.65 mmol, 71%) of product, mp 115-116.6° C

35 Calculated for C<sub>18</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub>:

C, 55.09; H, 7.19; N, 21.41

Found:

C, 55.20; H, 7.31; N, 21.10

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EXAMPLE 81

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2-Ethoxy-9-methoxymethyl-6-(1-piperazinyl)purine maleate

The foregoing material prepared in Example 80 (255 mg, 0.65 mmol) was dissolved in CF<sub>3</sub>COOH (4 ml) and stirred at room temperature for 40 min. The mixture was concentrated and to the residual oil was added a small amount of Dowex 1x2(OH) resin, followed by 1 drop of conc. NaOH (to ensure basicity). This total mixture was then poured onto a Dowex 1x2(OH) column and developed with H<sub>2</sub>O. Fractions containing the required product were pooled and evaporated to give 70 mg (0.24 mmol) of the title compound as the free base. This was dissolved in EtOH (2 ml) and 56 mg (0.49 mmol) of maleic acid in EtOH (3 ml) was added. The solution was concentrated under a stream of N<sub>2</sub> until precipitation was observed. This solid was removed by centrifugation and washed with Et<sub>2</sub>O (2 x 3 ml). Yield 81 mg (0.20 mmol), more product was apparent in the supernatants.

Calculated for  $C_{13}H_{25}N_5O_2 \cdot C_4H_4O_4$ :

C, 50.00; H, 5.92; N, 20.58

Found:

C, 49.94; H, 5.92; N, 20.55

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## EXAMPLE 82

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### 6-[1-(4-BOC)piperazinyl]-2-chloro-9-(ethoxymethyl)purine

The material prepared in Example 50 (847 mg, 2.5 mmol) was dissolved in sieve dried DMF (25 ml) and 60% NaH in oil (105 mg, 2.62 mmol of NaH) was added. After 20 minutes stirring under  $N_2$ , evolution of  $H_2$  had ceased and chloromethyl ethyl ether (0.255 ml, 2.75 mmol) was added. After 3 hrs at room temperature, tlc indicated complete reaction and the mixture was concentrated at  $65^\circ$  under a stream of  $N_2$  (with  $NaHCO_3$  outlet tube). The mixture was then evaporated to dryness and the residual oil was partitioned between  $CH_2Cl_2$  and 10% aqueous  $Na_2CO_3$ . The organic layer was dried ( $MgSO_4$ ), filtered, and evaporated to a viscous oil. This material was chromatographed on a silica gel 60 column (150 ml) packed in EtOAc : hexanes (1 : 4) and developed with a step gradient of EtOAc : hexanes (from 1 : 4 to 1 : 1). Fractions containing the required product were pooled and evaporated to dryness to give 620 mg (1.56 mmol, 62.5%) of the title compound, mp  $102-104^\circ C$ .

Calculated for  $C_{17}H_{25}N_5O_3Cl$ :

C, 51.45; H, 6.35; N, 21.18

Found:

C, 51.28; H, 6.42; N, 20.86

30

## EXAMPLE 83

### 6-[1-(4-BOC)piperazinyl]-9-ethoxymethyl-2-methoxypurine

The foregoing material prepared in Example 82 (300 mg, 0.75 mmol) was added to a solution of methanolic sodium methoxide (0.69 ml of 4.37M solution) in methanol (6 ml) and the mixture was heated under reflux under  $N_2$  for 42 hrs. The solution was then cooled and carefully neutralized with acetic acid before being evaporated to dryness. This residue was partitioned between  $CH_2Cl_2$  and 10% aqueous  $Na_2CO_3$  and the organic layer was dried ( $MgSO_4$ ), filtered and evaporated to dryness. This residue was purified by chromatography on a silica gel 60 column (50 ml) developed in EtOAc : hexanes (3 : 7) to give the title compound as a tlc pure viscous clear oil (259 mg, 0.66 mmol, 88%). Mass spec. (FAB) showed  $M^+ + H$  at 393 m/e.

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## EXAMPLE 84

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### 9-Ethoxymethyl-2-methoxy-6-(1-piperazinyl)purine maleate

The foregoing material prepared in Example 83 (170 mg, 0.43 mmol) was dissolved in  $CF_3COOH$  (3 ml) and stirred at room temperature for 30 min before being concentrated to dryness. To this residual liquid was added a small amount of Dowex 1x2(OH) resin in  $H_2O$  and the slurry was placed atop a Dowex 1x2-(OH) column which was then developed with  $H_2O$ . Fractions containing the required product were pooled and evaporated to dryness in vacuo to give 37 mg (0.13 mmol, 29%) of the product as its free base. This

was dissolved in EtOH (7 ml) containing maleic acid (29.9 mg, 0.26 mmol) and the solution was concentrated under a stream of N<sub>2</sub> to give a residual oil. Trituration under Et<sub>2</sub>O gave a gummy solid which was further washed with EtOAc to give 37.8 mg of the title compound. Mass spec. (EI) showed M<sup>+</sup> (free base) at 292 m/e.

5 Calculated for C<sub>13</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>:  
C, 49.99; H, 5.92; N, 20.58  
Found:  
C, 49.97; H, 5.66; N, 20.40

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EXAMPLE 85

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6-[1-(4-BOC)piperazinyl]-2-chloro-9-(cyclopropylmethyl)purine

The material prepared in Example 50 (1.02 g, 3.0 mmol) was dissolved in sieve dried DMF (25 ml) and 180 mg of 60% NaH in oil (4.5 mmol of NaH) was added. This mixture was stirred under N<sub>2</sub> until evolution of H<sub>2</sub> had ceased. Bromomethylcyclopropane (0.35 ml, 3.6 mmol) in DMF (0.5 ml) was added and the reaction was stirred at room temperature under N<sub>2</sub> overnight. The mixture was neutralized with acetic acid and evaporated to a semi-solid residue which was partitioned between EtOAc and 10% aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. This residue was chromatographed on silica gel 60 (dry packed) developing with a step gradient of EtOAc : hexanes (1:4) to EtOAc : hexanes (2:3) to give 1.007 g (2.56 mmol, 85%) of the title compound as a white solid, mp 141-143° C.

25 Calculated for C<sub>18</sub>H<sub>25</sub>N<sub>6</sub>O<sub>2</sub>Cl•0.1H<sub>2</sub>O:  
C, 54.78; H, 6.44; N, 21.29  
Found:  
C, 55.10; H, 6.48; N, 20.94

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EXAMPLE 86

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6-[1-(4-BOC)piperazinyl]-9-cyclopropylmethyl-2-ethoxypurine

Sodium spheres (120 mg, 5.2 mmol) were added to abs. EtOH (5 ml) and after hydrogen evolution had ceased, 517 mg (1.3 mmol) of material from the foregoing Example 85 in EtOH (95 ml) was added. This solution was heated under reflux under N<sub>2</sub> for 28 hrs. The mixture was neutralized with acetic acid and evaporated to a solid residue which was partitioned between EtOAc and 10% aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness to give 510 mg of a viscous oil. This was chromatographed on a dry packed silica gel 60 column (60 ml) which was developed with a step gradient of EtOAc : hexanes (1:4) to EtOAc : hexanes (2 : 3) in 10% increments. Fractions containing the required product were pooled and evaporated to dryness to give 389 mg (0.97 mmol, 74%) of the title compound as a white solid, mp 120-122° C. Mass spec (EI) showed M<sup>+</sup> at 402 m/e.

45 Calculated for C<sub>20</sub>H<sub>30</sub>N<sub>6</sub>O<sub>3</sub>:  
C, 59.68; H, 7.51; N, 20.88  
Found:  
C, 59.87; H, 7.65; N, 20.75

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EXAMPLE 87

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9-Cyclopropylmethyl-2-ethoxy-6-(1-piperazinyl)purine dihydrochloride

The foregoing material prepared in Example 86 (260 mg, 0.65 mmol) was dissolved in abs. EtOH (6 ml) and ethanolic HCl (2 ml) was added. This solution was concentrated slowly under a stream of N<sub>2</sub>. A white precipitate formed which was washed well with Et<sub>2</sub>O. Yield 222 mg (0.59 mmol, 92%). Mass spec (EI) showed M<sup>+</sup> (free base) at 302 m/e.

Calculated for C<sub>15</sub>H<sub>22</sub>N<sub>6</sub>O•2HCl:

C, 48.01; H, 6.45; N, 22.39

Found:

C, 48.17; H, 6.52; N, 22.29

EXAMPLE 886-[1-(4-BOC)piperazinyl]-2-chloro-9-(methoxyethyl)purine

The material prepared in Example 50 (1.02 g, 3.0 mmol) was dissolved in sieve dried DMF (25 ml) and 60% NaH in oil (180 mg, 4.5 mmol of NaH) was added and the mixture was stirred under N<sub>2</sub>. When a homogeneous solution was apparent 2-bromoethyl methyl ether (0.33 ml, 3.6 mmol) was added and the reaction was left stirring overnight. Additional 2-bromoethyl methyl ether (0.085 ml) was then added followed by sodium iodide (90 mg, 0.6 mmol). After stirring for an additional 24 hrs. the mixture was neutralized with acetic acid and evaporated to dryness in vacuo. The residue so obtained was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and the organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. Purification was carried out on a dry packed silica gel 60 column (70 ml) developing with a step gradient of (1 : 4) to (1 : 1) EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give (1.82 mmol, 61%) of the title compound as a tlc pure white solid. Mp 104-107° C, mass spec (EI) showed M<sup>+</sup> at 397 and 399 m/e.

Calculated for C<sub>17</sub>H<sub>25</sub>N<sub>6</sub>O<sub>3</sub>Cl:

C, 51.45; H, 6.35; N, 21.18

Found:

C, 51.63; H, 6.36; N, 21.03

EXAMPLE 896-(1-(4-BOC)piperazinyl)-2-methoxy-9-(methoxyethyl)purine

To a methanolic solution of sodium methoxide (0.75 ml of 4.37 M solution) in methanol (8 ml) was added 3.25 mg (0.82 mmol) of the foregoing material prepared in Example 88. This solution was heated under reflux under N<sub>2</sub> for 4 days. After evaporation to dryness, the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and the organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. Purification was carried out on a dry packed silica gel 60 column (40 ml) developing with a step gradient of (3 : 7) to (3 : 2) EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 192 mg of the title compound as a clear, tlc pure oil.

EXAMPLE 90

2-Methoxy-9-methoxyethyl-6-(1-piperazinyl)purine dihydrochloride

The foregoing material prepared in Example 89 (182 mg, 0.46 mmol) was dissolved in abs. EtOH (3 ml) and ethanolic HCl (1.5 ml) was added. After 2 hrs. the solution was concentrated under a stream of N<sub>2</sub> to give a white solid which was washed with Et<sub>2</sub>O and EtOH to give 109 mg of the title compound. Mass spec (EI) showed M<sup>+</sup> (free base) at 293 m/e.

Calculated for C<sub>13</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>•2HCl:

C, 42.75; H, 6.07, N, 23.01

Found:

C, 42.87, H, 6.09; N, 22.94

EXAMPLE 916-[1-(4-BOC)piperazinyl]-2-chloro-9-(methylthiomethyl)purine

The material prepared in Example 50 (1.02 g, 3.0 mmol) was dissolved in sieve dried DMF (25 ml) under N<sub>2</sub> and 60% NaH in oil (156 mg, 3.9 mmol of NaH) was added. After the evolution of H<sub>2</sub> had ceased, chloromethyl methyl sulfide (0.3 ml, 3.6 mmol) in DMF (3 ml) was added and the reaction was stirred at room temperature for 3 days. Cold H<sub>2</sub>O (25 ml) was carefully added, followed by 10 ml of 10% aqueous Na<sub>2</sub>CO<sub>3</sub>. After stirring for 1 hr the mixture was evaporated to dryness in *vacuo* and the residual solid was partitioned between EtOAc and 10% aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. The residue so obtained was purified by chromatography on a dry packed silica gel 60 column (960 ml) developed with a step gradient of (1:4 to 2:3) EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 625 mg (1.72 mmol, 57%) of the title compound as a white solid. Mp 144-145° C, mass spec (EI) showed M<sup>+</sup> at 398 m/e.

EXAMPLE 926-[1-(4-BOC)piperazinyl]-2-methoxy-9-(methylthiomethyl)purine

To a methanolic solution of sodium methoxide (0.76 ml of a 4.37 M solution) in methanol (8 ml) was added 301 mg (0.75 mmol) of the foregoing material prepared in Example 91. This solution was heated under reflux under N<sub>2</sub> for 2 days and then was cooled and neutralized with acetic acid before being evaporated to dryness. The solid so obtained was partitioned between EtOAc and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and the organic phase was dried (MgSO<sub>4</sub>) filtered and evaporated to dryness. Purification was carried out on a dry packed silica gel 60 column (40 ml) developed with a step gradient of EtOAc : hexanes (1: 4 to 1:1). Fractions containing the required product were pooled and evaporated to dryness to give 264 mg (0.67 mmol, 89%) of the title compound. Mp 138-139.5°, mass spec. (EI) showed M<sup>+</sup> at 394 m/e.

Calculated for C<sub>17</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub>S•0.1H<sub>2</sub>O:

C, 51.52; H, 6.67; N, 21.21

Found:

C, 51.91; H, 6.74; N, 20.88

EXAMPLE 93

2-Methoxy-9-(methylthiomethyl)-6-(1-piperaziny)purine maleate

The foregoing material prepared in Example 92 (253 mg, 0.64 mmol) was dissolved in CF<sub>3</sub>COOH (3 ml) and stirred at room temperature for 40 min. The mixture was concentrated under a stream of N<sub>2</sub> and a slurry of Dowex 1x2 (OH) in H<sub>2</sub>O was added to the residue. This mixture was poured onto a column (2.5 x 20 cm) of Dowex 1x2 (OH) and the column was developed with H<sub>2</sub>O. Fractions containing the required product were pooled and evaporated to dryness to give 91 mg (0.31 mmol) of the title compound as its free base. This was dissolved in EtOH (3 ml) and maleic acid (69 mg, 0.60 mmol) in EtOH (4 ml) was added. The solution was concentrated under a stream of N<sub>2</sub> and the precipitate obtained was separated and washed with Et<sub>2</sub>O. Yield 117.6 mg (0.29 mmol, 45%), mass spec. (EI) showed M<sup>+</sup> (free base) at 294 m e.

Calculated for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>SO•1.2 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>:

C, 46.53; H, 5.30; N, 19.38

Found:

C, 46.57; H, 5.44; N, 19.33

EXAMPLE 946-[1-(4-BOC)piperaziny]-2-chloro-9-[2-(trimethylsilyl)ethoxymethyl]purine

The material prepared in Example 50 (2.03 g, 6.0 mmol) was dissolved in sieve dried DMf (50 ml) and 60% NaH in oil (336 mg, 8.4 mmol of NaH) was added. This mixture was stirred under N<sub>2</sub> until hydrogen evolution had ceased and then 2-(trimethylsilyl)ethoxymethyl chloride (1.17 ml, 6.6 mmol) was added. The reaction was stirred under N<sub>2</sub> at room temperature for 24 hrs. and then cold H<sub>2</sub>O (50 ml) was added, followed by 10% aq. Na<sub>2</sub>CO<sub>3</sub> (20 ml). This mixture was evaporated to dryness and the solid residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aq. Na<sub>2</sub>CO<sub>3</sub>. To the organic phase was added a little EtOAc (to effect complete dissolution) and then it was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. Purification was carried out on a dry packed silica gel 60 column (3.5 x 25cm), developed with a step gradient (1 : 9 to 2 : 3) of EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 2.08g (4.43 mmol, 74%) of a white gummy solid. A portion was recrystallized from EtOH to give an analytical sample. Mp 127-128.5 °C

Calculated for C<sub>20</sub>H<sub>33</sub>N<sub>5</sub>O<sub>3</sub>ClSi:

C, 51.21; H, 7.09; N, 17.92

Found:

C, 51.30; H, 6.97; N, 17.95

EXAMPLE 956-[1-(4-BOC)piperaziny]-2-methoxy-9-[2-(trimethylsilyl)ethoxymethyl]purine

The foregoing material prepared in Example 94 (957 mg, 2.04 mmol) was added to a solution of 4.37 M methanolic sodium methoxide (1.87 ml) in MeOH (20 ml) and the mixture was heated under reflux under N<sub>2</sub> for 3 days. The mixture was neutralized with acetic acid and then evaporated to dryness to give a solid residue which was partitioned between EtOAc and 10% aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. This material was purified on a dry-packed silica gel 60 column (70 ml) developed with a step gradient of (1:4 to 2:3) of EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 794 mg (1.71 mmol, 84%) of the title compound as a white solid. Mp 109-110 °C.

Calculated for  $C_{21}H_{36}N_6O_4Si$ :

C, 54.29; H, 7.81; N, 18.09

Found:

C, 54.24; H, 7.87; N, 18.12

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#### EXAMPLE 96

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#### 6-[1-(4-BOC)piperazinyl]-2-methoxypurine

The foregoing material prepared in Example 95 (782 mg, 1.68 mmol) was dissolved in dry THF (9 ml) and 9 ml of a 1M solution of tetrabutylammonium fluoride in THF was added. This solution was heated at 60° overnight and then an additional 2 ml of 1M tetrabutylammoniumfluoride in THF was added and the heating was continued at 70° for an additional 6 hrs. This mixture was evaporated to dryness and the orange residual oil was purified on a dry packed silica gel 60 column (80 ml) developed with a step gradient (1 : 4 to 2 : 3) of acetone : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 358 mg (1.07 mmol, 64%) of the title compound as a tlc pure white solid.

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#### EXAMPLE 97

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#### 6-[1-(4-BOC)piperazinyl]-9-[1-(2-fluoroethyl)]-2-methoxypurine

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#### Method A

The foregoing material prepared in Example 96 (102.8 mg, 0.31 mmol) was dissolved in sieve dried DMF (3 ml) and stirred under  $N_2$ . To this solution was added 60% NaH in oil (16 mg, 0.4 mmol of NaH) and when  $H_2$  evolution had ceased, 1-bromo-2-fluoroethane (50 mg, 0.4 mmol) was added. After stirring overnight the mixture was neutralized with acetic acid and evaporated to dryness. This residue was partitioned between EtOAc and 10% aqueous  $Na_2CO_3$  and the organic phase was dried ( $MgSO_4$ ), filtered and evaporated to dryness. Purification was carried out on a dry-packed silica gel 60 column (30 ml) developed with a step gradient (3:7 to 3:2) of EtOAc : hexanes. Fractions containing the required product were pooled and evaporated to dryness to give 85.2 mg (0.23 mmol, 73%) of the title compound as a white solid. Mp 139.5-104.5° C.

40

Calculated for  $C_{17}H_{25}N_6OF \cdot 0.2 H_2O$ :

C, 53.31; H, 6.68; N, 21.94

Found:

C, 53.55; H, 6.56; N, 21.61

45

#### Method B

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A mixture of the material prepared in Example 117 (50 mg, 0.13 mmol) and methanol (0.5 ml) containing sodium methoxide (0.5 mmol) was refluxed under a nitrogen atmosphere for 18 hours. After cooling, the reaction treated with a mixture of 1M  $K_2PO_4$  and  $CHCl_3$ , and after thorough mixing the phases were separated. The aqueous phase was reextracted with  $CHCl_3$  and the organic phases dried ( $MgSO_4$ ) and evaporated to give 60 mg of a crystalline residue. Preparative tlc on one 20x20cm x1000 $\mu$  silica gel GF plate with (1:1) EtOAc : hexanes gave, after isolation, 17.5 mg of unreacted starting material and, 23.3 mg the title compound which was identical to material prepared by Method A.

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EXAMPLE 989-[1-(2-Fluoroethyl)]-2-methoxy-6-(1-piperaziny)purine dihydrochloride

The foregoing material prepared in Example 97 (78 mg, 0.26 mmol) was dissolved in abs. EtOH (4 ml) and 2 ml of ethanolic HCl was added. After standing at room temperature for 30 min the solution was slowly concentrated using a stream of N<sub>2</sub>. The white solid so obtained was washed with EtOH and Et<sub>2</sub>O and dried to give 58.9 mg (0.16 mmol, 62%) of the title compound.

Calculated for C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>OF•2HCL.0.2 CH<sub>3</sub>CH<sub>2</sub>OH:

C, 41.09; H, 5.67; N, 23.19

Found:

C, 40.86; H, 5.68; N, 22.85

The 0.2 molar equivalents of EtOH in the analytical sample were verified by NMR.

EXAMPLE 996-[1-(4-BOC)piperaziny]-2-methoxy-9-[1-(2-propynyl)]purine

The material prepared in Example 96 (150 mg, 0.45 mmol) was dissolved in sieve dried DMF (3 ml) and 60% NaH in oil (27 mg, 0.67 mmol of NaH) was added. This mixture was stirred under N<sub>2</sub> until hydrogen evolution had ceased and then propargyl bromide (80% by wt in toluene; 0.06 ml, 0.54 mmol) was added. The mixture was stirred at room temperature overnight under N<sub>2</sub> and then was neutralized with acetic acid before being evaporated to dryness. This solid residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aq. Na<sub>2</sub>CO<sub>3</sub> and the organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. Two products were apparent by tlc and these were separated on a dry packed silica gel 60 column (50 ml) developed with a step gradient of hexanes to acetone : hexanes (1 : 4). Fractions containing the slower moving material were pooled and evaporated to dryness to give 48 mg (0.13 mmol, 29%) of the title compound as a clear oil. Mass spec (EI) showed M<sup>+</sup> + H at 373 m/e and further identification was by PMR (see Table).

EXAMPLE 1009-(1-Allenyl)-6-[1-(4-BOC)piperaziny]-2-methoxypurine

Fractions containing the faster moving product from the silica gel 60 column described in the previous Example 99 were pooled and evaporated to dryness to give 66 mg (0.18 mmol, 39%) of the title compound as a white solid. Mass spec. (EI) showed M<sup>+</sup> + H at 373 m/e. Further identification was by PMR (see Table).

EXAMPLE 101

2-Methoxy-6-(1-piperaziny)-9-[1-(2-propynyl)]purine dihydrochloride

The material prepared in Example 99 (40 mg, 0.11 mmol) was deblocked in the usual way with ethanolic HCl to give 24 mg (0.07 mmol, 61%) of the title compound. Mass spec. (EI) showed  $M^+$  (free base) at 272 m/e.

Calculated for  $C_{13}H_{15}N_5O \cdot 2HCl \cdot 1.1 H_2O$ :

C, 42.77; H, 5.58; N, 23.02

Found:

C, 42.94; H, 5.11; N, 22.65

EXAMPLE 1029-(1-Allenyl)-2-methoxy-6-(1-piperaziny)purine dihydrochloride

The material prepared in Example 100 (63 mg, 0.17 mmol) was deblocked in the usual way with ethanolic HCl to give 60.2 mg (0.16 mmol, 97%) of the title compound. Mass spec. (EI) showed  $M^+ + H$  (free base) at 273 m/e.

Calculated for  $C_{13}H_{16}N_5O \cdot 2HCl \cdot 0.6 H_2O \cdot 0.25 CH_3CH_2OH$ :

C, 44.12; H, 5.68; N, 22.87

Found:

C, 44.03; H, 5.55; N, 22.85

The 0.25 molar equivalents of EtOH in the analytical sample were verified by NMR.

EXAMPLE 1036-[1-(4-BOC)piperaziny]-2-methoxy-9-[1-(2-propenyl)]purine

The material prepared in Example 96 (150 mg, 0.45 mmol) was dissolved in sieve dried DMF (8 ml) and 60% NaH in oil (27 mg, 0.68 mmol of NaH) was added. This mixture was stirred under  $N_2$  until evolution of hydrogen had ceased and then 3-iodopropene (0.05 ml, 0.55 mmol) was added. After stirring for 6 hrs. under  $N_2$  at room temperature, the mixture was evaporated to dryness in vacuo and the residue was partitioned between  $CH_2Cl_2$  (100 ml) and 10% aq.  $Na_2CO_3$  (20 ml). The organic phase was dried ( $MgSO_4$ ), filtered and evaporated to dryness. This residue was purified on a silica gel 60 column (15 g) developed with a step gradient of hexanes, EtOAc : hexanes (1:3), EtOAc : hexanes (1:1) and then EtOAc. Fractions containing the required product were pooled and evaporated to dryness to give 138 mg (0.37 mmol, 82%) of the title compound as a tlc pure syrup. Mass spec. (EI) showed  $M^+ + H$  at 375 m/e.

EXAMPLE 104

2-Methoxy-6-(1-piperazinyl)-9-[1-(2-propenyl)]purine dihydrochloride

The foregoing material prepared in Example 103 (133 mg, 0.36 mmol) was deblocked with ethanolic HCl in the usual way to give 101 mg (0.29 mmol, 81%) of the title compound.

Calculated for  $C_{13}H_{13}N_5O \cdot 2HCl$ :

C, 44.96; H, 5.81; N, 24.20

Found:

C, 45.22; H, 6.19; N, 24.00

EXAMPLE 1055-Amino-4-chloro-6-cyclopropylamino-2-ethylpyrimidine

A mixture of 4,6-dichloro-5-nitro-2-ethylpyrimidine (0.5 g), Raney nickel (ca. 0.5 g) and MeOH (5 ml) was shaken in a hydrogen atmosphere at 1-2 p.s.i until reduction of the nitro group was complete. The mixture was filtered, evaporated to a black gum, taken up in a mixture of cyclopropylamine (5 ml, ca. 100 mmol) and isopropyl alcohol (5 ml) and heated in a bomb at 110° for 4 hours. The reaction mixture was then filtered, evaporated to dryness under reduced pressure and the pure product was isolated by preparative tlc using four 20x20 cmx1000 $\mu$  silica gel GF plates developed with 1 : 1 EtOAc : hexanes; 315 mg of product was obtained. Yield: 64%. NMR ( $CDCl_3$ ,  $\delta$  from TMS): 0.47(m) and 0.76(m) cyclopropyl methylenes, 1.24 (t,  $CH_3$ ), 2.69 (q,  $\underline{CH_2}CH_3$ ), 2.86 (m, CH), 3.47 (br s,  $NH_2$ ), 5.47 (br s, NH).

EXAMPLE 1066-Chloro-9-cyclopropyl-2-ethylpurine

A mixture of the material prepared in the foregoing Example 105 (315 mg, 1.47 mmol), triethylorthoformate (3 ml), and conc. HCl (0.03 ml) was heated and stirred at 60°. After two hours the mixture was evaporated under a stream of nitrogen with heating. The solid brown residue was purified by preparative tlc on four 20x20cm x1000 $\mu$  silica gel GF plates developed with 10% MeOH in  $CH_2Cl_2$ . The main band was isolated and extracted to give 265 mg of the title compound as a crystalline solid. NMR ( $CDCl_3$ ,  $\delta$  from TMS): 1.12-1.30 (m, cyclopropyl methylenes), 1.41 (t,  $CH_3$ ), 3.07 (q,  $\underline{CH_2}CH_3$ ), 3.50 (m, CH), 8.03 (s, H8).

EXAMPLE 1076-[1-(4-BOC)piperazinyl]-9-cyclopropyl-2-ethylpurine

A mixture of the foregoing material prepared in Example 106 (249 mg, 1.2 mmol) 1-BOC piperazine (232 mg, 1.3 mmol) and triethylamine (0.35 ml, 2.5 mmol) in i-amyl alcohol (5 ml) were refluxed for 3 hours. The mixture was taken to dryness under reduced pressure and purified on four 20x20cm x1000 $\mu$  silica gel GF plates using 1:1 EtOAc : hexane. Isolation and extraction of the main band gave the title compound.

EXAMPLE 108

9-Cyclopropyl-2-ethyl-6-(1-piperazinyl)purine

A portion of the foregoing material prepared in Example 107 was dissolved in ca. 1 ml of  $\text{CF}_3\text{CO}_2\text{H}$ . After 15-20 minutes, the clear solution was evaporated to a gum under a nitrogen stream, and the residue was partitioned between water and chloroform. The aqueous phase was extracted a second time with chloroform and then made basic by careful addition of solid  $\text{K}_2\text{CO}_3$ . The milky aqueous solution was extracted repeatedly with chloroform and the combined organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated to dryness to give the title compound, which was crystallized from ether.

Calculated for  $\text{C}_{14}\text{H}_{20}\text{N}_6 \cdot 0.1 (\text{C}_2\text{H}_5)_2\text{O}$ :

C, 61.82; H, 7.57; N, 30.04

Found:

C, 61.45; H, 7.65; N, 29.85

EXAMPLE 1094-[1-(4-BOC)piperazinyl]-6-chloro-2-ethyl-5-nitropyrimidine

To a stirred solution of 4,6-dichloro-5-nitro-2-ethylpyrimidine (509 mg, 2.3 mmol) and triethylamine (0.35 ml, 2.5 mmol) in sieve dried DMF (4 ml) was added dropwise over 3 minutes a solution of BOC-piperazine (0.5 g, 2.7 mmol) in sieve dried DMF (2 ml). The mildly exothermic reaction was allowed to proceed for a few minutes longer after which time it was filtered and the filtrate evaporated to a gum under high vacuum. The residue was partitioned between  $\text{CHCl}_3$  and water, the aqueous phase extracted again with  $\text{CHCl}_3$ , the combined organic extracts washed once with water, once with saturated NaCl solution, dried ( $\text{MgSO}_4$ ) and evaporated to a dark foam. This residue was purified by preparative tlc on four 20x20cm x1000 $\mu$  silica gel of plates with 20% ethyl acetate in hexane. The main (high Rf) band of the four observed afforded 466 mg of the title compound as a yellow solid which was crystallized from hexane. NMR ( $\text{CDCl}_3$ ,  $\delta$  from TMS): 1.29 (t,  $\text{CH}_3$ ), 1.47 (s,  $\text{C}(\text{CH}_3)_3$ ), 2.80 (q,  $\text{CH}_2\text{CH}_3$ ), 3.58 (m, piperazine methylenes).

EXAMPLE 1104-[1-(4-BOC)piperazinyl]-2-ethyl-5-nitro-6-[1-(2,2,2-tri-fluoroethylamino)]pyrimidine

To a solution of the foregoing material prepared in Example 109 (418 mg, 1.3 mmol) and triethylamine (0.2 ml, 1.4 mmol) in sieve dried DMF (5 ml) was added dropwise, with stirring, a solution of 209 mg (2.1 mmol) of 2,2,2-trifluoroethylamine in sieve dried DMF (1 ml) over two minutes. No exotherm was noted. After standing 64 hours, the reaction mixture was evaporated to dryness under reduced pressure and the residue was partitioned between water and  $\text{CHCl}_3$ . The aqueous phase was extracted again with  $\text{CHCl}_3$ , and the combined organic phases were washed once with water, once with saturated NaCl solution, dried ( $\text{MgSO}_4$ ) and evaporated to a gum. This was purified on four 20x20cm x1000 $\mu$  silica gel GF plates using EtOAc : hexanes 1 : 4). Isolation and extraction of the main band gave 414 mg of the title compound suitable for further reactions. NMR ( $\text{CDCl}_3$ ,  $\delta$  from TMS): 1.24 (t,  $\text{CH}_2\text{CH}_3$ ), 1.49 (s,  $\text{C}(\text{CH}_3)_3$ ), 2.65 (q,  $\text{CH}_2\text{CH}_3$ ), 3.56 (br, s piperazine methylenes), 4.36 (m,  $\text{CH}_2\text{CF}_3$ ), 8.43 (t,  $\text{NHCH}_2$ ).

EXAMPLE 111

5-Amino-4-[1-(4-BOC)piperazinyl]-2-ethyl-6-[1-(2,2,2-trifluoroethylamino)]pyrimidine

A suspension of the foregoing material prepared in Example 110 (363 mg, 0.96 mmol) in MeOH (10 ml) containing 0.2-0.3 g Raney nickel, was shaken in a 1-2 p.s.i. atmosphere of hydrogen. After 24 hrs. the mixture was filtered (the organic material having now dissolved), evaporated and purified by preparative tlc on four 20x20cm x1000 $\mu$  silica gel GF plates using EtOAc : hexanes (1:4), to give ca. 0.2g of the title compound along with some recovered unreduced starting material. NMR (CDCl<sub>3</sub>,  $\delta$  from TMS): 1.25 (t, CH<sub>2</sub>CH<sub>3</sub>), 1.48 (s, C(CH<sub>3</sub>)<sub>3</sub>), 2.68 (q, CH<sub>2</sub>CH<sub>3</sub>), 2.97 (br s NH<sub>2</sub>), 3.14 (m) and 3.58 (m) (piperazine methylenes), 4.25 (m, CH<sub>2</sub>CF<sub>3</sub>), 4.53 (t, NHCH<sub>2</sub>).

EXAMPLE 1126-[1-(4-BOC)piperazinyl]-2-ethyl-9-[1-(2,2,2-trifluoroethylamino)]purine

To a solution of the foregoing material prepared in Example 111 (79 mg) in triethyl orthoformate (1.0 ml) stirred at 60° C was added concentrated HCl (0.01 ml). After 6 hrs, heating was stopped and the reaction was left standing at ambient temperature for ca. 12 hours. The solution was shaken with 1M K<sub>2</sub>HPO<sub>4</sub> (1 ml), the organic phase was removed, dried (MgSO<sub>4</sub>) and evaporated to a solid. The residue was purified by preparative tlc using two 20x20cm x1000 $\mu$  silica gel GF plates, developed with MeOH : CH<sub>2</sub>Cl<sub>2</sub> - (5:95). Isolation and extraction of the main band gave pure title compound. Further purification was effected by crystallization from hexanes.

EXAMPLE 1132-ethyl-9-[1-(2,2,2-trifluoroethylamino)]-6-(1-piperazinyl)purine

The foregoing material prepared in Example 112 (160 mg) was dissolved in ca. 2 ml of trifluoroacetic acid. After 30 minutes the solution was evaporated to a gum under a nitrogen stream and the residue was partitioned between water and CHCl<sub>3</sub>. The aqueous phase was separated, extracted a second time with CHCl<sub>3</sub>, then made basic by careful addition of solid K<sub>2</sub>CO<sub>3</sub>, and saturated with solid NaCl. The milky solution was extracted several times with CHCl<sub>3</sub> and the combined organic phases were washed once with saturated NaCl solution, dried (MgSO<sub>4</sub>) and evaporated to give 124 mg of a gum. Recrystallization from hexanes, after removal of a slight flocculant insoluble contaminant, gave 91 mg of the title compound. Mp 104-106° C.

Calculated for C<sub>13</sub>H<sub>17</sub>N<sub>5</sub>F<sub>3</sub>:

C, 49.67; H, 5.45; N, 26.74

Found:

C, 49.87; H, 5.56; N, 26.69

EXAMPLE 1146-[1-(4-BOC)piperazinyl]-2-chloro-9-[1-(2-oxopropyl)]purine

The material prepared in Example 50 (1.02g, 3.0 mmol) was dissolved in sieved-dried DMf 925 ml) and 60% NaH in oil (156 mg, 3.9 mmol of NaH) was added and the mixture was stirred under N<sub>2</sub> until evolution of H<sub>2</sub> had ceased. Chloroacetone (0.31 ml, 3.9 mmol) was then added and the mixture was stirred under N<sub>2</sub>

for 3 days. The reaction was evaporated to dryness and the residue was partitioned between EtOAc and 10% aq.  $\text{Na}_2\text{CO}_3$ . The organic phase was dried ( $\text{MgSO}_4$ ), filtered and evaporated to dryness to give 1.28 g of a pale yellow oil. Trituration under hexanes gave 1.07g of the title compound, mp 173-175 °C.

Calculated for  $\text{C}_{17}\text{H}_{23}\text{N}_6\text{OCl}$ :

5 C, 51.71; H, 5.87; N, 21.28

Found

C, 51.58; H, 5.87; N, 20.95

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#### EXAMPLE 115

#### 15 6-[1-(4-BOC)piperaziny]-2-chloro-9-[1-(2,2-difluoropropyl)]purine

A suspension of  $\text{MgO}$  (50 mg) in sieve dried  $\text{CH}_2\text{Cl}_2$  (1.1 ml) containing diethylaminosulfur trifluoride (0.1 ml, 0.8 mmol) was stirred while 315 mg (0.8 mmol) of the material prepared in Example 114 was added under nitrogen over 2-3 minutes. After 20 hours an additional 0.1 ml of diethylamino sulfurtrifluoride was added, and after four more hours the reaction was worked up. The mixture was added to 1M  $\text{K}_2\text{HPO}_4$  and the mix was extracted with several portions of  $\text{CHCl}_3$ . The pooled organic layers were dried ( $\text{MgSO}_4$ ), filtered and evaporated to give a semicrystalline product. Preparative tlc on four 20x20cm x1000 $\mu$  silica gel GF plates developed with EtOAc : hexanes (1 : 1) gave 60 mg of recovered starting ketone and 184 mg of the title compound.

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#### EXAMPLE 116

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#### 6-[1-(4-BOC)piperaziny]-9-[1-(2,2-difluoropropyl)]-2-methoxypurine

A mixture of the foregoing material prepared in Example 115 (50 mg, 0.12 mmol) and methanol (0.2 ml) containing ca. 0.4 mmol of sodium methoxide was refluxed under a nitrogen atmosphere for 18 hours. After cooling it was treated with a mixture of 1M  $\text{KH}_2\text{PO}_4$  and  $\text{CHCl}_3$  and after thorough mixing, the phases were separated. The aqueous phase was extracted again with  $\text{CHCl}_3$  and the combined organic extracts dried ( $\text{MgSO}_4$ ) and evaporated to give 44 mg of a semicrystalline residue. Preparative tlc on one 20x20cm x1000 $\mu$  silica gel GF plate developed with EtOAc : hexanes (1:1) gave 6.4 mg of starting material and 29.1 mg of the title compound as a gum which crystallized upon trituration under ether.

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#### EXAMPLE 117

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#### 6-[1-(4-BOC)piperaziny]-2-chloro-9-[1-(2-fluoroethyl)]purine

The material prepared in Example 50 (300 mg, 0.89 mmol) was dissolved in sieve dried DMF (5 ml) and 60% NaH in oil (1.5 mmol) of NaH was added. This mixture was stirred under  $\text{N}_2$  until evolution of  $\text{H}_2$  had ceased (2 1/2hr). The mixture was centrifuged and the supernatant was added dropwise to a stirred solution of 1-bromo-2-fluoroethane (7.9 mmol) in 1 ml of sieve dried DMF. After stirring overnight at room temperature under  $\text{N}_2$ , the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and sat. aq.  $\text{NaHCO}_3$ . The aqu. layer was further washed with  $\text{CH}_2\text{Cl}_2$  and the pooled organic layers were dried ( $\text{MgSO}_4$ ), filtered and evaporated to dryness. Purification was effected on four 20x20cm x1000 $\mu$  silica gel GF preparative plates developed with EtOAc : hexanes (1:1). The title compound was obtained as a crystalline solid after standing under  $\text{Et}_2\text{O}$ .

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EXAMPLE 1186-Chloro-2-ethyl-9-methylpurine

This was prepared in a manner similar to that described in Example 27 for 6-chloro-2,9-dimethylpurine, except that 5-amino-4-chloro-2-ethyl-6-methylaminopyrimidine was used as the starting material, and the final product was purified by chromatography. The title compound was obtained in 65% yield. NMR (CDCl<sub>3</sub>,  $\delta$  from TMS): 1.40 (t, CH<sub>2</sub>CH<sub>3</sub>), 3.06 (q, CH<sub>2</sub>CH<sub>3</sub>), 3.88 (s, NCH<sub>3</sub>), 8.00 (s, H<sub>8</sub>).

EXAMPLE 1196-[1-(4-BOC)piperaziny]-2-ethyl-9-methylpurine

This was prepared in a manner similar to that described in Example 28 for 6-[1-(4-BOC)piperaziny]-2,9-dimethylpurine, except that the foregoing material prepared in Example 118 (332 mg, 1.68 mmol) was used as the starting material. The title compound was obtained in good yield after purification on four 20x20cmx1000 $\mu$  silica GF plates developed with CHCl<sub>3</sub> : MeOH : NH<sub>4</sub>OH (90 : 10 : 1)

EXAMPLE 1202-Ethyl-9-methyl-6-(1-piperaziny)purine dihydrochloride

The foregoing material prepared in Example 119 (300 mg, 0.87 mmol) was deblocked in the usual fashion using ethanolic HCl to give the title compound (197 mg, 0.62 mmol, 71%) as a white crystalline solid.

Calculated for C<sub>12</sub>H<sub>18</sub>N<sub>6</sub>•2HCl:

C, 45.15; H, 6.32; N, 26.33; Cl, 22.21

Found:

C, 45.20; H, 6.24; N, 26.53; Cl, 22.41

EXAMPLE 1216-[1-(4-BOC)piperaziny]-2-chloro-9-(2-propyl)purine

This was prepared in a manner similar to that described in Example 74 for 6-[1-(4-BOC)piperaziny]-2-chloro-9-(1-propyl)purine, except that 2-iodopropane was used as the alkylating agent. The reaction utilized 678 mg (2.0 mmol) of 6-[1-(4-BOC)piperaziny]-2-chloropurine as starting material and gave the title compound (640 mg, 1.68 mmol) in 84% yield after silica gel chromatography. Mass spec. (EI) showed M<sup>+</sup> at 380 and 382 m/e.

Calculated for C<sub>17</sub>H<sub>25</sub>N<sub>6</sub>O<sub>2</sub>Cl:

C, 53.61; H, 6.62; N, 22.06

Found:

C, 53.61; H, 6.59; N, 22.06

EXAMPLE 1226-[1-(4-BOC)piperazinyl]-2-methoxy-9-(2-propyl)purine

This was prepared in a manner similar to that described in Example 75 for 6-[1-(4-BOC)piperazinyl]-2-methoxy-9-(1-propyl)purine, except that the foregoing material described in Example 121 (305 mg, 0.8 mmol) was used as the starting material. The title compound was obtained as a crystalline solid (200 mg, 0.53 mmol, 66%) without recourse to chromatographic purification. Mass spec. (EI) showed  $M^+$  at 376 m/e.

Calculated for  $C_{18}H_{28}N_6O_3$ :

C, 57.43; H, 7.50; N, 22.33

Found:

C, 57.30; H, 7.46; N, 22.32

EXAMPLE 1232-Methoxy-6-(1-piperazinyl)-9-(2-propyl)purine dihydrochloride

The foregoing material prepared in Example 122 (150 mg, 0.40 mmol) was deblocked in the usual fashion using ethanolic HCl to give the title compound (89.4 mg, 0.26 mmol; 64%) as a white solid. Mass spec. (EI) showed  $M^+$  (free base) at 276 m/e.

Calculated for  $C_{13}H_{20}N_6O \cdot 2HCl \cdot 0.2H_2O$ :

C, 44.25; H, 6.40; N, 23.82

Found:

C, 44.24; H, 6.30; N, 23.59

EXAMPLE 1246-[1-(4-BOC)piperazinyl]-2-methoxy-9-[1-(2-oxopropyl)]purine

The material prepared in Example 96 (84 mg, 0.25 mmol) was dissolved in sieve dried DMf (2 ml) and 60% NaH in oil (15 mg, 0.38 mmol of NaH) was added. This mixture was stirred under  $N_2$  under evolution of  $H_2$  had ceased. Chloroacetone (0.03 ml, 0.38 mmol) was then added and the stirring was evaporated to dryness and the residue was partitioned between EtOAc and 10% aq.  $Na_2CO_3$ . The organic phase was dried ( $MgSO_4$ ), filtered and evaporated to an oil. This was purified on a dry packed silica gel 60 column (25 ml) developed with a step gradient (3:7 to 7:3) of EtOAc : hexanes to give 80 mg (0.2 mmol, 80%) of the title compound as a chromatographically pure oil which crystallized upon trituration.

EXAMPLE 125



2-Methoxy-9-[1-(2-oxopropyl)]-6-(1-piperazinyl)purine dihydrochloride

The foregoing material prepared in Example 124 (65 mg, 0.17 mmol) was deblocked using ethanolic HCl in the usual fashion to give the title compound (25.7 mg, 0.07 mmol, 43%) as a white solid. Mass spec.

(EI) showed  $M^+$  (free base) at 290 m/e.

Calculated for  $C_{13}H_{18}N_6O \cdot 2HCl \cdot H_2O$ :

C, 40.96; H, 5.82; N, 22.04

Found:

C, 40.76; H, 5.69; N, 22.04

EXAMPLE 1269-[1-(2,2-Difluoropropyl)]-2-methoxy-6-(1-piperazinyl)purine dihydrochloride

The material prepared in Example 116 (96 mg, 0.23 mmol) was deblocked in the usual fashion using ethanolic HCl (6.5 ml) to give the title compound (59.8 mg, 0.15 mmol, 65%) as a white crystalline solid.

Calculated for  $C_{13}H_{18}N_6OF_2 \cdot 0.7H_2O \cdot 2HCl$ :

C, 39.24; H, 5.42; N, 21.13; Cl, 17.82

Found:

C, 39.03; H, 5.34; N, 21.34; Cl, 17.92

EXAMPLE 1275-Amino-4,6-dichloro-2-ethylpyrimidine

4,6-Dichloro-5-nitro-2-ethylpyrimidine (185 g, 0.83 mol) was dissolved in methanol (1.5L) and reduced under 15 p.s.i.  $H_2$  in the presence of Raney nickel (30 g) for 5hr. The mixture was filtered through Celite (washing well with MeOH) and the filtrate was evaporated to dryness to give 159.1 g (0.83 mol, quantitative yield) of the title compound as a chromatographically pure (silica gel plates, developed with EtOAc : hexanes, 3:1) dark liquid which was used directly in the next step.

EXAMPLE 1286-Chloro-5,6-diamino-2-ethylpyrimidine

The material prepared in the foregoing Example 127 (6.19 g, 32 mmol) was dissolved in 2-propanol (75 ml) and 10 ml of anhydrous ammonia was added. This was sealed in a pressure vessel and heated at  $110^\circ$  for 4 hr. The mixture was vented and then evaporated to a solid residue under a stream of nitrogen. This residue was leached with  $CH_2Cl_2$  (3 x 10 ml) and the soluble material (3g) was shown (tlc, EtOAc : hexanes, 1 : 1) to be predominantly unreacted starting material, whereas the insoluble material (3.29g, 19 mmol) was chromatographically pure title compound, suitable for the next reaction (Yield, 60%; quantitative, based on recovered starting material).

EXAMPLE 129

6-Chloro-2-ethylpurine

The material prepared in the foregoing Example 128 (1.50g, 8.72 mmol) and triethylorthoformate (15 ml) were mixed and heated at 60° for 1 hr. Concentrated HCl (0.15 ml) was added and the heating was continued overnight. After cooling to room temperature the suspension was filtered off and the solid was washed with Et<sub>2</sub>O. This solid product (1.1g) was essentially chromatographically pure (silica gel; CHCl<sub>3</sub> : MeOH : NH<sub>4</sub>OH - 90 : 10 : 1). An analytical sample was prepared by recrystallization from MeOH. NMR (DMSO-d<sub>6</sub>,  $\delta$  from TMS): 1.31 (t, CH<sub>2</sub>CH<sub>3</sub>), 3.95 (q, CH<sub>2</sub>CH<sub>3</sub>), 8.57 (s, H8).

Calculated for C<sub>7</sub>H<sub>7</sub>N<sub>4</sub>Cl:

C, 46.04; H, 3.86; N, 30.68; Cl, 19.41

Found:

C, 45.45; H, 3.98; N, 30.38; Cl, 19.91

EXAMPLE 1306-[1-(4-BOC)piperazinyl]-2-ethylpurine

The material prepared in the foregoing Example 129 (1.75g, 9.6 mmol), BOC-piperazine (1.97g, 11 mmol), triethylamine (2.8 ml, 20 mmol) and i-amyl alcohol (20 ml) were mixed and heated under reflux under N<sub>2</sub> for 3 hr. The mixture was allowed to cool and the solid was filtered off and washed with a small portion of i-amyl alcohol and then with Et<sub>2</sub>O. Yield 2.1g, 66%.

EXAMPLE 1316-[1-(4-BOC)piperazinyl]-2-ethyl-9-(2-fluoroethyl)purine

The material prepared in the foregoing Example 130 (401 mg, 1.21 mmol) was dissolved in sieve dried DMF (5 ml) and 60% NaH in oil, 73 mg, 1.8 mmol of NaH) was added. This mixture was stirred under N<sub>2</sub> until the hydrogen evolution had ceased. The mixture was centrifuged and the supernatant was added dropwise, with stirring, to a solution of 1-bromo-2-fluoroethane (1.002g, 7.89 mmol) in sieve dried DMF (1 ml). This mixture was stirred under N<sub>2</sub> overnight and then was evaporated to dryness in vacuo. The residue was partitioned between 1M KH<sub>2</sub>PO<sub>4</sub> and CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous phase was washed once more with CH<sub>2</sub>Cl<sub>2</sub>. The pooled organic layers were washed with H<sub>2</sub>O and sat. aq. NaCl, and then dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness (531 mg). This was purified on four 20 x 20 cm x 1000 $\mu$  silica gel GF plates developed with EtOAc : hexanes (1:2) to give 445 mg (1.18 mmol, 97%) of the title compound.

EXAMPLE 1322-Ethyl-9-(2-fluoroethyl)-6-(1-piperazinyl)purine dihydrochloride

The material prepared in the foregoing Example 131 (339 mg, 0.90 mmol) was deblocked in the usual fashion using ethanolic HCl (2.0 ml) to give the title compound (149 mg, 0.4 mmol, 44%) as a white crystalline solid.

Calculated for  $C_{13}H_{19}N_5 \cdot 2HCl$ :

C, 41.27; H, 6.27; N, 22.21; Cl, 20.15

Found:

C, 41.02; H, 6.37; N, 22.35; Cl, 20.02

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### EXAMPLE 133

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#### 2-Methoxy-6-(1-piperazinyl)-9-(2-furanylmethyl)-9H-purine

To 2-methoxy-6-[1-(4-tertbutoxycarbonyl)-piperazinyl]-9H-purine (1.05g., 3.1 mMol) in DMF (10 ml.,  
 15 sieve dried) at 0 ° C under  $N_2$  was added sodium hydride (60% dispersion) (0.25 g., 6.3 mMol). The mixture was washed to RT, and after stirring at 25 ° for 2 hours, the solution was centrifuged. The brown solution was then added dropwise over 5 minutes to a solution of 2-chloromethylfuran (W.R. Kirner, J. Am. Chem. Soc., 50, 1958 (1928)) (0.44 g., 3.8 mMol) in DMF (1 ml) at 0 ° C. After allowing to warm to RT overnight, the DMF was removed in vacuo over a 60 ° bath. The mixture was acidified with a saturated solution of  $KH_2PO_4$   
 20 (25 ml), and the mixture was extracted with chloroform (3x25 ml). The combined extracts were dried over  $MgSO_4$  and the solvent was removed in vacuo to leave a light tan oil (2.0 g); nmr ( $CDCl_3$ )  $\delta$ : 1.43(9H, S), 3.52(4H, m), 3.95(3H, s), 4.22 (4H, m), 5.23(2H, s), 6.32(1H, m), 6.37(1H, d), 7.37(1H, d), 7.61(1H, s), contained 1.0 eq. of DMF; mass spectrum (FAB): 415.

The crude oil (2.0 g) was dissolved in a mixture 1N-HCl (12 ml) and acetonitrile (12 ml). After 2 hours at  
 25 RT the solvent was partially removed in vacuo and dried under a stream of  $N_2$ . The residue was dissolved in  $H_2O$  (50 ml), decolorized with Darco and made basic to pH 12 with 10% NaOH. The product was extracted with  $CHCl_3$  (3X25 ml), dried over  $Na_2SO_4$  and concentrated to a light oil (0.8 g) of 2-methoxy-6-(1-piperazinyl)-9-(2-furanylmethyl)-9H-purine; nmr ( $CDCl_3$ )  $\delta$ : 2.94(4H, m), 3.94(3H, s), 4.22(4H, bd. m), 5.23-  
 (2H, s), 6.31(1H, m), 6.36(1H, d), 7.35(1H, d), 7.59(1H, s); mass spectrum (FAB): 3.15.

30 Anal. Calcd. for  $C_{15}H_{18}N_5O_2 \cdot 0.56 H_2O$ :

C, 55.54; H, 5.94; N, 25.91

Found:

C, 55.56; H, 5.95; N, 25.82.

A portion of oil was dissolved in three fold excess of 4N ethanolic HCl. The solution was concentrated in  
 35 vacuo to remove excess HCl and the product was triturated with  $Et_2O$ -EtOH to yield a crystalline salt: mp. 174 ° dec.; nmr ( $D_2O$ )  $\delta$ : 3.52(4H, m), 4.10(3H, s), 4.53(4H, m), 5.44(2H, s), 6.54(1H, m), 6.63(1H, d), 7.59-  
 (1H, s), 8.18(1H, d).

Anal. Calcd. for  $C_{15}H_{18}N_5O_2 \cdot 2HCl \cdot 1.5 H_2O$ :

C, 43.49, H, 5.60; N, 20.28

40 Found:

C, 43.70; H, 5.62; N, 20.37.

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TABLE 1

## PROTON NMR SHIFT DATA FOR 6-(1-PIPERAZINYL)PURINES

Example	Piperazine Methylene Resonances	Heterocyclic Protons	Others
1 <sup>a</sup>	3.60(m), 4.25(m)	7.95(s), 8.39(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub>
2 <sup>a</sup>	3.50(m), 4.30(m)	7.70(s), 8.38(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.82(s)-N9-CH <sub>3</sub>
3 <sup>a</sup>	3.60(m), 4.00(m)	7.85(s), 8.0(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.50(m)-N3-CH <sub>3</sub>
4 <sup>b</sup>	3.55(m), 4.55(m)	8.25(s), 8.43(s)	3.90(s)-N9-CH <sub>3</sub>
7 <sup>a</sup>	3.60(m), 4.30(m)	7.70(s), 8.10(s)	2.95(s) 3.65-4.00(m) 4.35(s) 4.40(d) 5.00(s) 5.15(s) 5.70(d) 6.50(d) 7.40(m)
8 <sup>b</sup>	3.60(m), 3.90(m) 4.10(m)	8.20(s), 8.30(s)	2.90(m) 4.12(m) 4.40(m) 6.00(d) 7.40(m)
11 <sup>a</sup>	3.58(m), 4.29(m)	8.29(s)	1.46(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.60(s)-C8-CH <sub>3</sub>
12 <sup>b</sup>	3.59(m), 4.29(m)	8.30(s)	2.67(s)-C8-CH <sub>3</sub>
14 <sup>a</sup>	3.55(m), 4.70(m)	8.25(s)	1.42(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.50(s)-C8-CH <sub>3</sub> 3.68(s)-C9-CH <sub>3</sub>
15 <sup>b</sup>	3.55(m), 4.42(m)	8.36(s)	2.62(s)-C8-CH <sub>3</sub> 3.78(s)-C9-CH <sub>3</sub>

TABLE 1 (Cont'd)

5	Example	Piperazine Methylene Resonances	Heterocyclic Protons	Others
	22 <sup>a</sup>	3.47(m), 4.13(m)	8.22(s)	1.41(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.47(s)-N9-CH <sub>3</sub>
10	23 <sup>b</sup>	3.44(m), 4.40(m)	8.32(s)	3.74(s)-N9-CH <sub>3</sub>
	24 <sup>a</sup>	3.59(m), 4.29(m)	8.32(s)	1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
	25 <sup>a</sup>	3.42(m), 4.06(m)	7.99(s)	1.44(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.34(d)-C8-NHCH <sub>3</sub>
15	26 <sup>b</sup>	3.55(m), 4.54(m)	8.44(s)	
	28 <sup>a</sup>	3.56(m), 4.26(m)	7.64(s)	1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.58(s)-C2-CH <sub>3</sub>
20	29 <sup>a</sup>	3.56(m), 4.20(m)		3.78(s)-N9-CH <sub>3</sub> 1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.54(s)-C2-CH <sub>3</sub>
25	30 <sup>a</sup>	3.54(m), 4.16(m)		3.72(s)-N9-CH <sub>3</sub> 1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.52(s)-C2-CH <sub>3</sub> 3.09(d)-C8-NHCH <sub>3</sub>
30	31 <sup>a</sup>	3.44(m), 4.08(m)		3.46(s)-N9-CH <sub>3</sub> 1.38(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.42(s)-C2-CH <sub>3</sub> 2.83(s)-C8-N(CH <sub>3</sub> ) <sub>2</sub>
35	32 <sup>b</sup>	3.53(m), 4.36(m)		3.50(s)-N9-CH <sub>3</sub> 2.50(s)-C2-CH <sub>3</sub> 3.15(s)-C8-NHCH <sub>3</sub>
40	33 <sup>a</sup>	3.36-3.50(m), 4.06(m)		3.62(s)-N9-CH <sub>3</sub> 1.38(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.85(m)-(CH <sub>2</sub> ) <sub>2</sub> - 2.42(s)-C2-CH <sub>3</sub> 3.36-3.50(m)-
45				CH <sub>2</sub> NCH <sub>2</sub> - 3.54(s)-N9-CH <sub>3</sub>
50				
55				

TABLE 1 (Cont'd)

Example	Piperazine Methylene Resonances	Heterocyclic Protons	Others
34 <sup>a</sup>	3.44(m), 4.04(m)		1.40(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.43(s)-C2-CH <sub>3</sub> 3.20(s)-C8-OCH <sub>3</sub> 4.00(s)-N9-CH <sub>3</sub>
35 <sup>b</sup>	3.50(m), 4.46(m)		2.68(s)-C2-CH <sub>3</sub> 3.13(s)-C8-N(CH <sub>3</sub> ) <sub>2</sub> 3.76(s)-N9-CH <sub>3</sub>
36 <sup>b</sup>	3.50(m), 4.28(m)		2.08(m)-(CH <sub>2</sub> ) <sub>2</sub> - 2.67(s)-C2-CH <sub>3</sub> 3.78-3.98(m)- -CH <sub>2</sub> NCH <sub>2</sub> -, N9-CH <sub>3</sub>
37 <sup>a</sup>	3.42-3.54(m), 4.02-4.16(m)	8.20(s)	1.42(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.48(s)-C8-OCH <sub>3</sub> 4.08(s)-N9-CH <sub>3</sub>
38 <sup>a</sup>	3.53(m), 4.18(m)	8.24(s)	1.47(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.95(s)-C8-N(CH <sub>3</sub> ) <sub>2</sub> 3.62(s)-N9-CH <sub>3</sub>
39 <sup>b</sup>	2.89(m), 3.88-4.14(m)	8.15(s)	3.43(s)-C8-OCH <sub>3</sub> 3.88-4.14(s)-N9-CH <sub>3</sub> 1.42(s)-C(CH <sub>3</sub> ) <sub>3</sub>
40 <sup>a</sup>	3.40-3.60(m), 4.51(m)	8.14(s)	1.92(m)-(CH <sub>2</sub> ) <sub>2</sub> - 3.40-3.60(m)- -CH <sub>2</sub> NCH <sub>2</sub> -
41 <sup>a</sup>	3.56(m), 4.25(m)	8.28(s)	4.62(s)-N9-CH <sub>3</sub> 1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.72(s)-C8-SCH <sub>3</sub>
42 <sup>b</sup>	3.56(m), 4.20(m)	8.48(s)	3.65(s)-N9-CH <sub>3</sub> 2.17(m)-(CH <sub>2</sub> ) <sub>2</sub> - 3.97(m)-N9-CH <sub>3</sub> , -CH <sub>2</sub> NCH <sub>2</sub> -

TABLE 1 (Cont'd)

Example	Piperazine Methylene	Heterocyclic	Others
	Resonances	Protons	
43 <sup>b</sup>	3.56(m), 4.38(m)	8.46(s)	3.27(s)-C8-N(CH <sub>3</sub> ) <sub>2</sub> 3.86(s)-N9-CH <sub>3</sub>
45 <sup>a</sup>	3.56(m), 4.24(m)		1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.52(s)-C2 or C8-CH <sub>3</sub> 2.56(s)-C2 or C8-CH <sub>3</sub> 3.68(s)-N9-CH <sub>3</sub> 2.60(s)-C2 or C8-CH <sub>3</sub> 2.65(s)-C2 or C8-CH <sub>3</sub> 3.74(s)-N9-CH <sub>3</sub>
46 <sup>b</sup>	3.46(m), 4.55(m)		1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.62(s)-C2/C8-CH <sub>3</sub> 's 2.61(s)-C2 or C8-CH <sub>3</sub> 2.64(s)-C2 or C8-CH <sub>3</sub> 1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub>
48 <sup>a</sup>	3.57(m), 4.28(m)		
49 <sup>b</sup>	3.49(m), 4.45(m)		
50 <sup>a</sup>	3.58(m), 3.80-4.80(br)	7.88(s)	
51 <sup>a</sup>	3.46(m) 3.80-4.80(br)	8.17(s)	1.43(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.69(s)-N9-CH <sub>3</sub>
52 <sup>b</sup>	3.44(m), 4.42(m)	8.03(s)	3.72(s)-N9-CH <sub>3</sub>
53 <sup>a</sup>	3.53(m), 4.17(m)	7.45(s)	1.47(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.64(s)-N9-CH <sub>3</sub> 3.75(s)-morpholine CH <sub>2</sub> 's 3.74(s)-N9-CH <sub>3</sub> 3.80(m)-morpholine CH <sub>2</sub> 's
54 <sup>b</sup>	3.40(m), 4.38(m)	8.00(s)	

TABLE 1 (Cont'd)

	Example	Piperazine Methylene	Heterocyclic	Others
		Resonances	Protons	
5	55 <sup>a</sup>	3.48-3.62(m), 4.19(m)	7.40(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.94(m)-(CH <sub>2</sub> ) <sub>2</sub> - 3.66(s)-N9-CH <sub>3</sub> 3.48-3.62(m)-
10				-CH <sub>2</sub> NCH <sub>2</sub> - 2.06(m)-(CH <sub>2</sub> ) <sub>2</sub> - 3.62(m)-CH <sub>2</sub> NCH <sub>2</sub> -
15	56 <sup>b</sup>	3.46(m), 4.53	7.82(s)	3.81(s)-N9-CH <sub>3</sub>
20	57 <sup>a</sup>	3.54(m), 4.20(m)	7.42(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.00(d)-C2-NHCH <sub>3</sub> 3.66(s)-N9-CH <sub>3</sub>
25	58 <sup>b</sup>	3.48(m), 4.57(m)	7.84(s)	3.02(s)-C2-NHCH <sub>3</sub>
	59 <sup>a</sup>	3.54(m), 4.19(m)	7.41(s)	3.78(s)-N9-CH <sub>3</sub>
30	60 <sup>b</sup>	3.46(m), 4.52(m)	7.88(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
35	61 <sup>a</sup>	3.54(m), 4.13(m)		3.17(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
40	62 <sup>a</sup>	3.48-3.60(m) 4.14(m)		3.66(s)-N9-CH <sub>3</sub>
45	62 <sup>b</sup>	2.84-2.96(m), 4.03(m)		3.26(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
50				3.84(s)-N9-CH <sub>3</sub>
55				1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
				3.16(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
				3.60(s)-N9-CH <sub>3</sub>
				1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
				2.88(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
				3.16(s)-C8-N(CH <sub>3</sub> ) <sub>2</sub>
				3.53(s)-N9-CH <sub>3</sub>
				2.90(m)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
				3.10(s)-C8-N(CH <sub>3</sub> ) <sub>2</sub>



TABLE 1 (Cont'd)

Example	Piperazine Methylene	Heterocyclic	Others
	Resonances	Protons	
64 <sup>a</sup>	3.54(m), 4.24(m)	7.56(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
			3.73(s)-N9-CH <sub>3</sub>
			3.96(s)-C2-OCH <sub>3</sub>
65 <sup>b</sup>	3.42(m), 4.44(m)	8.00(s)	3.72(s)-N9-CH <sub>3</sub>
			4.00(s)-C2-OCH <sub>3</sub>
66 <sup>a</sup>	3.54(m), 4.23(m)	7.54(s)	1.38(d)-OCH(CH <sub>3</sub> ) <sub>2</sub>
			1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
			3.70(s)-N9-CH <sub>3</sub>
			5.26(m)-C2-OCH-
67 <sup>b</sup>	3.48(m), 4.52(m)	8.10(s)	1.40(d)-OCH(CH <sub>3</sub> ) <sub>2</sub>
			3.80(s)-N9-CH <sub>3</sub>
			5.42(m)-C2-OCH-
			3.52(s)-N9-CH <sub>3</sub>
68 <sup>a</sup>	3.56(m), 4.24(m)	7.55(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
			3.21(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
69 <sup>b</sup>	3.46(m), 4.48(m)	7.97(s)	3.24(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
71 <sup>b</sup>	3.28-3.38(m),	7.98(s)	3.01(s)-NCH <sub>3</sub>
	3.60-3.80(m),		3.25(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
	5.28-5.42(m)		
72 <sup>b</sup>	2.80(m), 4.43(m)	7.42(s)	2.50(s)-NCH <sub>3</sub>
			3.17(s)-C2-N(CH <sub>3</sub> ) <sub>2</sub>
			3.66(s)-N9-CH <sub>3</sub>
73 <sup>b</sup>	3.46(m), 4.46(m)	8.00(s)	
74 <sup>a</sup>	3.58(m), 4.28(m)	7.69(s)	0.95(t)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
			1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
			1.90(m)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
			4.12(t)-NCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>

TABLE 1 (Cont'd)

5	Example	Piperazine Methylene	Heterocyclic	Others
		Resonances	Protons	
	75 <sup>a</sup>	3.58(m), 4.27(m)	7.59(s)	0.96(t)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
				1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub>
10				1.89(m)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
				3.97(s)-OCH <sub>3</sub>
				4.08(t)-NCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
15	76 <sup>b</sup>	3.46(m), 4.48(m)	8.12(s)	0.88(t)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
				1.86(m)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
				4.03(s)-OCH <sub>3</sub>
				4.14(t)-NCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
20	77 <sup>a</sup>	3.57(m), 4.26(m)	7.61(s)	0.94(t)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
				1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
				1.89(m)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
25				2.57(s)-SCH <sub>3</sub>
				4.10(t)-NCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
	78 <sup>b</sup>	3.44(m), 4.46(m)	8.05(s)	0.86(t)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
30				1.84(m)-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
				2.59(s)-SCH <sub>3</sub>
				4.12(t)-NCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
35	79 <sup>a</sup>	3.60(m), 4.30(m)	7.86(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub>
				3.38(s)-OCH <sub>3</sub>
				5.51(s)-NCH <sub>2</sub> O
40	80 <sup>a</sup>	3.58(m), 4.17(m)	8.72(s)	1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
				2.43(t)-CH <sub>2</sub> CH <sub>3</sub>
				3.37(s)-OCH <sub>3</sub>
				4.49(q)-CH <sub>2</sub> CH <sub>3</sub>
45				5.46(s)-NCH <sub>2</sub> O

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TABLE 1 (Cont'd)

Example	Piperazine Methylene	Heterocyclic	Others
	Resonances	Protons	
81 <sup>b</sup>	3.36-3.50(m), 4.32-4.49(m)	8.09(s)	1.38(t)-CH <sub>2</sub> CH <sub>3</sub> 3.39(s)-OCH <sub>3</sub> 5.52(s)-NCH <sub>2</sub> O 6.27(s)-CHCOO
82 <sup>a</sup>	3.52-3.64(m), 4.29(br m)	7.87(s)	1.19(t)-OCH <sub>2</sub> CH <sub>3</sub> 1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.52-3.64-OCH <sub>2</sub> CH <sub>3</sub> (overlap with piperazine)
83 <sup>a</sup>	3.50-3.66(m), 4.16-4.40(br m)	7.76(s)	5.55(s)-NCH <sub>2</sub> O 1.18(s)-OCH <sub>2</sub> CH <sub>3</sub> 1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.50-3.66-OCH <sub>2</sub> CH <sub>3</sub> (overlap with piperazine)
84 <sup>b</sup>	3.45(m), 4.46(m)	8.12(s)	3.98(s)-OCH <sub>3</sub> 5.52(s)-NCH <sub>2</sub> O 1.17(t)-OCH <sub>2</sub> CH <sub>3</sub> 3.68(q)-OCH <sub>2</sub> CH <sub>3</sub> 4.00(s)-OCH <sub>3</sub> 5.59(s)-NCH <sub>2</sub> O 6.26(s)-OHCOO
85 <sup>a</sup>	3.58(m), 4.19(br m)	7.82(s)	0.44(m) and 0.68(m), cyclopropyl methylenes 1.44-1.22(m)-CH 1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
86 <sup>a</sup>	3.58(m), 4.27(br m)	7.70(s)	4.01(d)-NCH <sub>2</sub> 0.43(m) and 0.64(m) cyclopropyl methylenes 1.22-1.38(m)-CH

TABLE I (Cont'd)

Example	Piperazine Methylene Resonances	Heterocyclic Protons	Others
5			1.42(t)-OCH <sub>2</sub> CH <sub>3</sub>
			1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
10			3.96(d)-NCH <sub>2</sub>
			4.40(q)-OCH <sub>2</sub> CH <sub>3</sub>
	87 <sup>b</sup>	8.24(s)	0.46(m) and 0.67(m), cyclopropyl methylenes
15			1.26-1.44(m)-CH
			1.40(t)-OCH <sub>2</sub> CH <sub>3</sub>
			4.04(d)-NCH <sub>2</sub>
20			4.48(q)-OCH <sub>2</sub> CH <sub>3</sub>
			(overlap with piperazine)
	88 <sup>a</sup>	7.82(s)	1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
25			3.34(s)-OCH <sub>3</sub>
			3.70(t)-NCH <sub>2</sub> CH <sub>2</sub> O
			4.18-4.40-NCH <sub>2</sub> CH <sub>2</sub> O
			(overlap with piperazine)
30			1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub>
	89 <sup>a</sup>	7.70(s)	3.33(s)-OCH <sub>3</sub>
			3.70(t)-NCH <sub>2</sub> CH <sub>2</sub> O
35			3.96(s)-C <sub>2</sub> -OCH <sub>3</sub>
			4.16-4.38-NCH <sub>2</sub> CH <sub>2</sub> O
			(overlap with piperazine)
40			3.36(s)-OCH <sub>3</sub>
	90 <sup>b</sup>	8.10(s)	3.86(t)-NCH <sub>2</sub> CH <sub>2</sub> O
			4.04(s)-C <sub>2</sub> -OCH <sub>3</sub>
45			4.40(t)-NCH <sub>2</sub> CH <sub>2</sub> O

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TABLE 1 (Cont'd)

<u>Example</u>	<u>Piperazine Methylene Resonances</u>	<u>Heterocyclic Protons</u>	<u>Others</u>
91 <sup>a</sup>	3.59(m), 4.28(br m)	7.91(s)	1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.14(s)-SCH <sub>3</sub> 5.17(s)-NCH <sub>2</sub> S
92 <sup>a</sup>	3.58(m), 4.27(br m)	7.77(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.15(s)-SCH <sub>3</sub> 3.97(s)-OCH <sub>3</sub> 5.15(s)-NCH <sub>2</sub> S
93 <sup>b</sup>	3.46(m), 4.45(m)	8.09(s)	2.14(s)-SCH <sub>3</sub> 3.98(s)-OCH <sub>3</sub> 5.22(s)-NCH <sub>2</sub> S 6.27(s)-CHCOO
94 <sup>a</sup>	3.56-3.70(m), 4.30(br m)	7.87(s)	-0.02(s)-Si(CH <sub>3</sub> ) <sub>3</sub> 0.85(d of d)-CH <sub>2</sub> Si 1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 3.56-3.70-OCH <sub>2</sub> CH <sub>2</sub> (overlap with piperazine)
95 <sup>a</sup>	3.52-3.68(m), 4.27(br m)	7.73(s)	5.55(s)-NCH <sub>2</sub> O -0.04(s)-Si(CH <sub>3</sub> ) <sub>3</sub> 0.92(d of d) -CH <sub>2</sub> Si 1.48(s) -C(CH <sub>3</sub> ) <sub>3</sub> 3.52-3.68 -OCH <sub>2</sub> CH <sub>2</sub> (overlap with piperazine)
96 <sup>a</sup>	3.60(m), 4.31 (br m)	7.77(s)	3.97(s)-OCH <sub>3</sub> 5.51(s)-NCH <sub>2</sub> O 1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 4.00(s) -OCH <sub>3</sub>

TABLE 1 (Cont'd)

5	Example	Piperazine Methylene	Heterocyclic	Others
		Resonances	Protons	
	97 <sup>a</sup>	3.58(m), 4.18-4.52(br m)	7.66(s)	1.49(s) -C(CH <sub>3</sub> ) <sub>3</sub> 3.95(s) -OCH <sub>3</sub> 4.18-4.52(d of t) -NCH <sub>2</sub> (overlap with piperazine) 4.74(d of t) -CH <sub>2</sub> F
10				
15	98 <sup>b</sup>	3.48(m), 4.42-4.64(m)	8.10(s)	4.02(s) -OCH <sub>3</sub> 4.42-4.64(d of t) -NCH <sub>2</sub> (overlap with piperazine) 4.84(d of t) -CH <sub>2</sub> F
20	99 <sup>a</sup>	3.58(m), 4.28(br m)	7.82(s)	1.49(s) -C(CH <sub>3</sub> ) <sub>3</sub> 2.49(t) -CH 3.98(s) -OCH <sub>3</sub>
25				
	100 <sup>a</sup>	3.58(m), 4.26(br m)	7.73(s)	4.90(d) -NCH <sub>2</sub> 1.49(s) -C(CH <sub>3</sub> ) <sub>3</sub> 3.98(s) -OCH <sub>3</sub> 5.66(d) -CH <sub>2</sub> 7.31(t) -NCH
30				
	101 <sup>b</sup>	3.43(m), 4.44(m)	8.08(s)	2.90(t) -CH 3.98(s) -OCH <sub>3</sub> 4.90(br s) -NCH <sub>2</sub>
35				
	102 <sup>b</sup>	3.44(m), 4.42(m)	8.00(s)	3.98(s) -OCH <sub>3</sub> 5.78(d) -CH <sub>2</sub> 7.10(t) -NCH
40				
	103 <sup>a</sup>	3.58(m), 4.28(br m)	7.59(s)	1.48(s) -C(CH <sub>3</sub> ) <sub>3</sub> 3.86(s) -OCH <sub>3</sub> 4.72(d of t) -NCH <sub>2</sub> 5.13-5.33(m) -CH=CH <sub>2</sub> 6.03(m) -CH
45				
50				

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TABLE 1 (Cont'd)

Example	<u>Piperazine Methylene</u>	<u>Heterocyclic</u>	<u>Others</u>
	<u>Resonances</u>	<u>Protons</u>	
104 <sup>b</sup>	3.46(m), 4.49(m)	8.06(s)	4.01(s)-OCH <sub>3</sub> 4.72-4.84-NCH <sub>2</sub> (overlap with H <sub>2</sub> O) 4.96-5.34(m)-CH=CH <sub>2</sub> 6.06(m)-CH
107 <sup>a</sup>	3.57(m), 4.28(m)	7.65(s)	1.0-1.23(m)-cyclopropyl methylenes 1.35(t)-CH <sub>3</sub> 1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.86(q)-CH <sub>2</sub> CH <sub>3</sub> 3.38-3.50(m)-NCH
108 <sup>a</sup>	3.00(m), 4.27(m)	7.64(s)	0.99-1.22(m)-cyclopropyl methylenes 1.34(t)-CH <sub>3</sub> 2.84(q)-CH <sub>2</sub> CH <sub>3</sub> 3.42(m)-NCH
112 <sup>a</sup>	3.59(m), 4.30(m)	7.77(s)	1.34(t)-CH <sub>2</sub> CH <sub>3</sub> 1.51(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.83(q)-CH <sub>2</sub> CH <sub>3</sub> 4.80(q)-CH <sub>2</sub> CF <sub>3</sub>
113 <sup>a</sup>	3.03(m), 4.30(m)	7.75(s)	1.33(t)-CH <sub>2</sub> CH <sub>3</sub> 2.82(q)-CH <sub>2</sub> CH <sub>3</sub> 4.79(q)-CH <sub>2</sub> CF <sub>3</sub>
114 <sup>a</sup>	3.59(m), 4.29(br m)	7.70(s)	1.49(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.31(s)-COCH <sub>3</sub> 5.00(s)-NCH <sub>2</sub> CO

TABLE 1 (Cont'd)

Example	Piperazine Methylene Resonances	Heterocyclic Protons	Others
115 <sup>a</sup>	3.59(m), 4.2 br m)	7.79(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.63(t)-CF <sub>2</sub> CH <sub>3</sub> 4.51(t)-NCH <sub>2</sub> CF <sub>2</sub>
116 <sup>a</sup>	3.57(m), 4.26(br m)	7.66(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.58(t)-CF <sub>2</sub> CH <sub>3</sub> 3.96(s)-OCH <sub>3</sub> 4.46(t)NCH <sub>2</sub> CF <sub>2</sub>
117	3.55(m), 4.26(br m)	7.76(s)	1.88(s)-C(CH <sub>3</sub> ) <sub>3</sub> 4.44(d of t)-NCH <sub>2</sub> CH <sub>2</sub> F 4.72(d of t)-NCH <sub>2</sub> CH <sub>2</sub> F
119 <sup>a</sup>	3.57(m), 4.28(m)	7.65(s)	1.33(t)-CH <sub>2</sub> CH <sub>3</sub> 1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.84(q)-CH <sub>2</sub> CH <sub>3</sub>
120 <sup>b</sup>	3.59(m), 4.72(m)	8.22(s)	3.79(s)-NCH <sub>3</sub> 1.43(t)-CH <sub>2</sub> CH <sub>3</sub> 3.05(q)-CH <sub>2</sub> CH <sub>3</sub> 3.97(s)-NCH <sub>3</sub>
121 <sup>a</sup>	3.58(m), 4.26(br m)	7.77(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.56(d)-CH(CH <sub>3</sub> ) <sub>2</sub> 4.84(m)-CH(CH <sub>3</sub> ) <sub>2</sub>
122 <sup>a</sup>	3.54(m), 4.04(br m)	7.63(s)	1.48(s)-C(CH <sub>3</sub> ) <sub>3</sub> 1.55(d)-CH(CH <sub>3</sub> ) <sub>2</sub> 3.94(s)-OCH <sub>3</sub>
123 <sup>b</sup>	3.43(m), 4.44(m)	8.06(s)	4.74(m)-CH(CH <sub>3</sub> ) <sub>2</sub> 1.54(d)-CH(CH <sub>3</sub> ) <sub>2</sub> 3.97(s)-OCH <sub>3</sub> 4.68(m)-CH(CH <sub>3</sub> ) <sub>2</sub>



TABLE 1 (Cont'd)

Example	Piperazine Methylene Resonances	Heterocyclic Protons	Others
124 <sup>a</sup>	3.59(m), 4.28(br m)	7.59(s)	1.50(s)-C(CH <sub>3</sub> ) <sub>3</sub> 2.28(s)-COCH <sub>3</sub> 3.95(s)-OCH <sub>3</sub> 4.94(s)-NCH <sub>2</sub> CO
125 <sup>b</sup>	3.42(m), 4.45(m)	7.88(s)	2.37(s) -COCH <sub>3</sub> 3.94(s) -OCH <sub>3</sub> 5.22(s) -NCH <sub>2</sub> CO
126 <sup>b</sup>	3.53(m), 4.56(m)	8.15(s)	1.82(t) -CF <sub>2</sub> CH <sub>3</sub> 4.09(s) -OCH <sub>3</sub> 4.62(t) -NCH <sub>2</sub> CF <sub>2</sub>
130 <sup>a</sup>	3.60(m), 4.35(m)	7.85(s)	1.41(t) -CH <sub>2</sub> CH <sub>3</sub> 1.49(s) -C(CH <sub>3</sub> ) <sub>3</sub> 2.92(q) -CH <sub>2</sub> CH <sub>3</sub>
131 <sup>a</sup>	3.59(m), 4.31(m)	7.77(s)	1.33(t) -CH <sub>2</sub> CH <sub>3</sub> 1.50(s) -C(CH <sub>3</sub> ) <sub>3</sub> 2.82(q) -CH <sub>2</sub> CH <sub>3</sub> 4.48(d of t) -NCH <sub>2</sub> CH <sub>2</sub> F 6.77(d of t) -NCH <sub>2</sub> CH <sub>2</sub> F
132 <sup>b</sup>	3.58(m), 4.60-5.14(m)	8.31(s)	1.42(t) -CH <sub>2</sub> CH <sub>3</sub> 3.03(q) -CH <sub>2</sub> CH <sub>3</sub> 4.60-5.14(m) -NCH <sub>2</sub> CH <sub>2</sub> F (overlap with piperazine and H <sub>2</sub> O).

All measured at 200 MHz in <sup>a</sup>CDCl<sub>3</sub> or <sup>b</sup>D<sub>2</sub>O

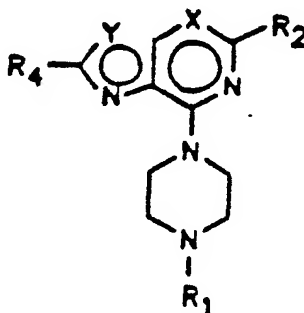
Chemical shifts in δ ppm from TMS (CDCl<sub>3</sub>) or TSP (D<sub>2</sub>O)

TABLE 2

PROPERTIES OF OTHER ALKYL 6-(1-PIPERAZINYL)PURINES		
Substituent	Salt Form	200 MHz Proton NMR -(D <sub>2</sub> O, $\delta$ from TSP)
2-methyl	diHCl	2.66 (s, 3), 3.51 (m, 4), 4.54 (m, 4), 8.22 (s, 1)
2,9-dimethyl	diHCl	2.70 (s, 3), 3.52 (m, 4), 3.90 (s, 3), 4.62 (m, 4), 8.16 (s, 1)
3-methyl	diHCl•0.33 H <sub>2</sub> O	3.52 (m, 4), 4.10 (s, 3), 4.52 (m, 4), 9.40 (s, 1), 8.56 (s, 1)
3-ethyl	diHCl•0.5H <sub>2</sub> O	1.58 (t, 3), 3.56 (m, 4), 4.58 (m, 6), 8.41 (s, 1), 8.61 (s, 1)
4',9-dimethyl	diHCl•0.5H <sub>2</sub> O	3.02 (s, 3), 3.32 (t, 2), 3.78 (m, 4), 3.90 (s, 3), 5.38 (d, 2), 8.24 (s, 1), 8.46 (s, 1)
9-ethyl	diHCl	1.49 (t, 3), 3.58 (m, 4), 4.34 (q, 2), 4.58 (m, 4), 8.38 (s, 1), 8.48 (s, 1)
9-isopropyl	diHCl•0.33 H <sub>2</sub> O	1.60 (d, 6), 3.55 (m, 4), 4.80 (hept, 1), 8.39 (s, 1), 8.41 (s, 1)
9-benzyl	diHCl	3.52 (m, 4), 4.52 (m, 4), 5.50 (s, 2), 7.35 (m, 5), 8.30 (s, 1), 8.40 (s, 1)

### Claims

1. A compound having the formula:



wherein X, and Y have the following meanings:

X	Y
N-(R <sub>3</sub> ) <sub>m</sub>	N-(R <sub>3</sub> ) <sub>n</sub>
CR <sub>3</sub>	N-R <sub>3</sub>
N	S
N	O

and R<sub>1</sub> and R<sub>3</sub> are independently hydrogen, loweralkyl, cycloloweralkyl, loweralkenyl, loweralkoxyloweralkyl, loweralkenyl, loweralkynyl, or phenylloweralkyl or substituted loweralkyl where the substituent is from 1 to 3 of halogen, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, loweralkylamino or diloweralkylamino, or the substituent is one of a 5- or 6-membered heteroaromatic ring system with nitrogen, oxygen or sulfur as the heteroatom, and m and n are 0 or 1 such that when m is 0, n is 1 and when m is 1, n is 0:

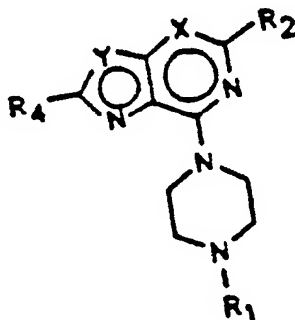
R<sub>2</sub> and R<sub>4</sub> are independently hydrogen, loweralkyl, cycloloweralkyl, loweralkoxy, loweralkylthio, loweralkyl-

sulfinyl, loweralkylsulfonyl, loweralkenyl, loweralkenyloxy, loweralkynyl, mono, di, or trihaloloweralkyl, phenyl or substituted phenyl where the substituent is from 1 to 3 of halo or loweralkyl, phenyloweralkyl, amino, loweralkylamino or dialkylamino where the alkyl groups can be linear, branched or joined in a ring of 5- or 6-members optionally containing oxygen or nitrogen as a heteroatom; and the pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein  $R_1$  is hydrogen, loweralkyl, or loweralkenyl;  $R_2$  is loweralkyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or pyrrolidino; each  $R_3$  is independently hydrogen, loweralkyl, loweralkoxyloweralkyl, or halogenated loweralkyl.

3. The compound of Claim 2 wherein  $R_1$  is hydrogen, methyl, ethyl or 2-propenyl;  $R_2$  is methyl, ethyl, methoxy, ethoxy, amino, methylamino, dimethylamino, pyrrolidino or ethylamino; each  $R_3$  is independently hydrogen, methyl, ethyl, n-propyl, isopropyl, methoxymethyl, methoxyethyl or fluoroethyl; and each  $R_4$  is independently hydrogen, methyl, methylamino, or dimethylamino.

4. The compound of Claim 1 having the formula



wherein Y is S or N- $R_3$  and the corresponding X is N or C- $R_3$ , and  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are as defined in Claim 1.

5. The compound of Claim 3 wherein X and Y are independently N and N- $R_3$ .

6. The compound of Claim 5 wherein X is N and Y is N- $R_3$ .

7. The compound of Claim 6 wherein  $R_3$  is a halogenated branched loweralkyl.

8. The compound of Claim 7 wherein  $R_3$  is a halogenated isopropyl group.

9. The compound of Claim 8 wherein  $R_3$  is a fluorinated isopropyl group.

10. The compound of Claim 9 wherein  $R_3$  is 1,3-difluoro isopropyl.

11. The compound of Claim 5 wherein  $R_1$  is hydrogen or methyl, and  $R_2$  and  $R_4$  are independently hydrogen, methyl, methoxy, ethoxy or dimethylamino.

12. The compound of Claim 1 which is X = N, Y = N-CH<sub>3</sub>,  $R_1$  = H,  $R_2$  = CH<sub>2</sub>CH<sub>3</sub> and  $R_4$  = H.

13. The compound of Claim 1 which is X = N, Y = N-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,  $R_1$  = H,  $R_2$  = OMe and  $R_4$  = H.

14. The compound of Claim 1 which is X = N, Y = N-CH<sub>2</sub>OCH<sub>3</sub>,  $R_1$  = H,  $R_2$  = OCH<sub>2</sub>CH<sub>3</sub> and  $R_4$  = H.

15. The compound of Claim 1 which is X = N, Y = N-CH<sub>2</sub>CH<sub>2</sub>F,  $R_1$  = H,  $R_2$  = OCH<sub>3</sub> and  $R_4$  = H.

16. The compound of Claim 1 which is X = N, Y = N-CH<sub>2</sub>CH<sub>2</sub>F,  $R_1$  = H,  $R_2$  = CH<sub>2</sub>CH<sub>3</sub> and  $R_4$  = H.

17. The compound of Claim 1 which is X = N, Y = NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>F,  $R_1$  = H,  $R_2$  = OCH<sub>3</sub> and  $R_4$  = H.

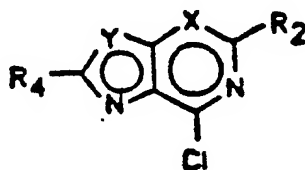
18. The compound of Claim 1 which is X = N, Y = NCH(CH<sub>3</sub>)<sub>2</sub>,  $R_1$  = H,  $R_2$  = OCH<sub>3</sub> and  $R_4$  = H.

19. The compound of Claim 1 which is X = N, Y = NCH(CH<sub>2</sub>F)<sub>2</sub>,  $R_1$  = H,  $R_2$  = OCH<sub>3</sub> and  $R_4$  = H.

20. The compound of Claim 1 which is X = NCH(CH<sub>2</sub>F)<sub>2</sub>,  $R_1$  = H,  $R_2$  = OCH<sub>2</sub>CH<sub>3</sub> and  $R_4$  = N.

21. The compound of Claim 1 which is X = N, Y = NCH(CH<sub>2</sub>F)<sub>2</sub>,  $R_1$  = H,  $R_2$  = CH<sub>2</sub>CH<sub>3</sub> and  $R_4$  = H.

22. A process for the preparation of a compound of Claim 1 which comprises treating a compound having the formula:



with an  $R_1$  substituted piperazine, or a protected piperazine wherein  $R_1$  is hydrogen, wherein X, Y,  $R_1$ ,  $R_2$  and  $R_3$  are defined above.

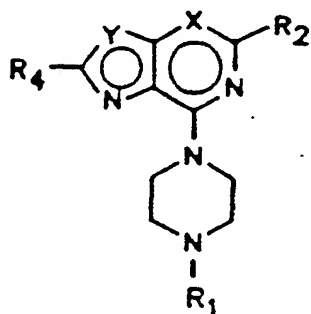
23. The process of Claim 22 wherein the piperazine is used in at least a 1 molar excess.

24. The use of a compound as claimed in Claim 1 for the preparation of a medicament useful for the treatment of diabetes or obesity with associated insulin resistance.

25. A composition useful for the treatment of diabetes or obesity with associated insulin resistance which comprises an inert carrier and a compound of Claim 1.

Claims for the following Contracting States: ES, GR

1.- A process for preparing piperazinyl derivatives of purines and isosteres thereof having the formula (I)



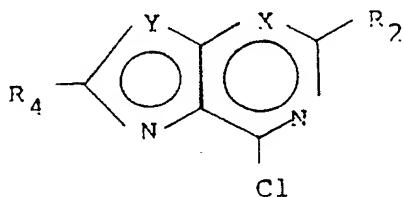
( I )

wherein X, and Y have the following meanings:

X	Y
N-( $R_3$ ) <sub>m</sub>	N-( $R_3$ ) <sub>n</sub>
CR <sub>3</sub>	N-R <sub>3</sub>
N	S
N	O

and  $R_1$  and  $R_3$  are independently hydrogen, loweralkyl, loweralkenyl, lower alkoxyloweralkyl, haloloweralkyl, loweralkenyl, loweralkynyl, or phenylloweralkyl and m and n are 0 or 1 such that when m is 0, n is 1 and when m is 1, n is 0;

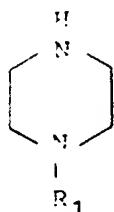
$R_2$  and  $R_4$  are independently hydrogen, loweralkyl, loweralkoxy, loweralkylthio, loweralkenyl, loweralkynyl-haloloweralkyl, phenylloweralkyl amino, loweralkylamino or dialkylamino where the alkyl groups can be linear, branched or joined in a ring of 5- or 6-members optionally containing oxygen or nitrogen as a heteroatom; and the pharmaceutically acceptable salts thereof, characterized by treating a compound of formula (II)



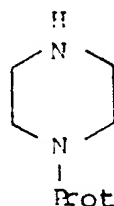
( II )

wherein  $R_2$ ,  $R_4$ , X and Y are those defined above,

a) with an  $R_1$  substituted piperazine of formula



wherein  $R_1$  is that defined above, in order to directly render compound I; or  
b) with a protected piperazine of formula



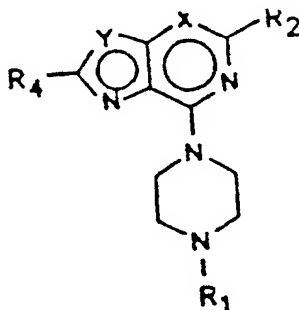
wherein  $Prot$  is a protecting group; followed by, further removal of the protecting group to render a compound of formula (I) wherein  $R_1$  is H, and then, optionally, if desired, further introduction of the  $R_1$  group.

2. The process of claim 1 wherein the piperazine is used in at least a 1 molar excess.

3. The process of Claim 1 wherein  $R_1$  is hydrogen, loweralkyl, or loweralkenyl;  $R_2$  is diloweralkylamino or pyrrolidino; each  $R_3$  is independently hydrogen, loweralkyl, loweralkoxyloweralkyl, or halogenated loweralkyl.

4. The process of claim 1 wherein  $R_1$  is hydrogen, methyl, ethyl or 2-propenyl;  $R_2$  is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, pyrrolidino or ethylamino; each  $R_3$  is independently hydrogen, methyl, ethyl, n-propyl, isopropyl, methoxymethyl, methoxyethyl or fluoroethyl; and each  $R_4$  is independently hydrogen, methyl, methylamino, or dimethylamino.

5. The process of claim 1 wherein the compound obtained has the formula



wherein Y is S or N- $R_3$  and the corresponding X is N or C- $R_3$ , and  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are as defined in claim 1.

6. The process of claim 5, wherein X and Y are independently N and N- $R_3$ .

7. The process of Claim 6 wherein  $R_3$  is a halogenated branched loweralkyl.

8. The process of Claim 7 wherein  $R_3$  is a halogenated isopropyl group.

9. The process of Claim 8 wherein  $R_3$  is a fluorinated isopropyl group.

10. The compound of Claim 9 wherein  $R_3$  is 1,3-difluoro isopropyl.

11. The process of claim 5 wherein  $R_1$  is hydrogen or methyl,  $R_3$  is methyl or ethyl and  $R_2$  and  $R_4$  are independently hydrogen, methyl, methoxy, ethoxy or dimethylamino.

12. The process of claim 1 which is X=N, Y=N- $CH_3$ ,  $R_1$ =H,  $R_2$ = $CH_2CH_3$ ,  $R_4$ =H.

13. The process of Claim 1 which is X=N, Y=N- $CH_2CH_2CH_3$ ,  $R_1$ =H,  $R_2$ =OMe and  $R_4$ =H.

14. The process of Claim 1 which is  $X = N$ ,  $Y = N-CH_2OCH_3$ ,  $R_1 = H$ ,  $R_2 = OCH_2CH_3$  and  $R_4 = H$ .  
15. The process of Claim 1 which is  $X = N$ ,  $Y = N-CH_2CH_2F$ ,  $R_1 = H$ ,  $R_2 = OCH_3$  and  $R_4 = H$ .  
16. The process of Claim 1 which is  $X = N$ ,  $Y = N-CH_2CH_2F$ ,  $R_1 = H$ ,  $R_2 = CH_2CH_3$  and  $R_4 = H$ .  
17. The process of Claim 1 which is  $X = N$ ,  $Y = NCH_2CH_2CH_2F$ ,  $R_1 = H$ ,  $R_2 = OCH_3$  and  $R_4 = H$ .  
18. The process of Claim 1 which is  $X = N$ ,  $Y = NCH(CH_3)_2$ ,  $R_1 = H$ ,  $R_2 = OCH_3$  and  $R_4 = H$ .  
19. The process of Claim 1 which is  $X = N$ ,  $Y = NCH(CH_2F)_2$ ,  $R_1 = H$ ,  $R_2 = OCH_3$  and  $R_4 = H$ .  
20. The process of Claim 1 which is  $X = NCH(CH_2F)_2$ ,  $R_1 = H$ ,  $R_2 = OCH_2CH_3$  and  $R_4 = N$ .  
21. The process of Claim 1 which is  $X = N$ ,  $Y = NCH(CH_2F)_2$ ,  $R_1 = H$ ,  $R_2 = CH_2CH_3$  and  $R_4 = H$ .



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 88306584.9
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP - A1 - 0 168 500 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) * Examples 2,4; page 11, lines 23-26; page 12, lines 7-11, 19-22,25,26 * --	1-5,11	C 07 D 473/34 C 07 D 471/04 A 61 K 31/52 A 61 K 31/44
A	DE - B2 - 1 695 821 (SCIENCE UNION ET CIE.) * Claims 1-7 * --	1-5,11	
A	DE - B - 1 115 260 (DR. KARL THOMAE GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG) * Compound no. 34 * --	1-5	
A	DE - A - 1 670 940 (FISONS PEST CONTROL LTD.) * Page 2, formula; page 3, lines 5-7; page 4, lines 1,2 * ----	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)  C 07 D 473/00 C 07 D 471/00
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 20-09-1988	Examiner HERING
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

(12)

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(71) Applicant: **JANSSEN PHARMACEUTICA N.V., Turnhoutseweg 30, B-2340 Beerse (BE)**

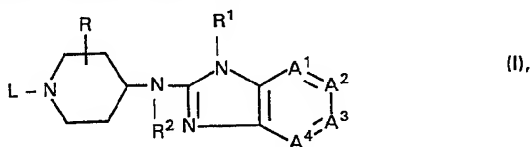
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(72) Inventor: **Janssens, Frans E., Tinststraat 79, B-2830 Bonheiden (BE)**  
 Inventor: **Hens, Jozef F., Rector de Ramstraat 54, B-2260 Nijlen (BE)**  
 Inventor: **Torremans, Joseph L.G., Lijsterstraat 11, B-2340 Beerse (BE)**  
 Inventor: **Heykants, Jozef J.P., Karel Druytslaan 9, B-2350 Vosselaar (BE)**

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(54) **Anti-histaminic compositions containing N-heterocyclyl-4-piperidinamines.**

(57) Anti-histaminic compositions containing as active ingredient a N-heterocyclyl-4-piperidinamine of formula



wherein,

L is hydrogen, C<sub>1-6</sub>alkyloxycarbonyl or phenylmethoxycarbonyl;

A<sup>1</sup> = A<sup>2</sup> - A<sup>3</sup> = A<sup>4</sup> is a bivalent radical having the formula

- CH = CH - CH = CH - (a),
- N = CH - CH = CH - (b),
- CH = N - CH = CH - (c),
- CH = CH - N = CH - (d), or
- CH = CH - CH = N - (e),

a pharmaceutically acceptable acid addition salt and possible stereochemically isomeric form thereof; methods of preparing said compounds and pharmaceutical compositions; novel compounds of formula (I).



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ANTI-HISTAMINIC COMPOSITIONS CONTAINING N-HETEROCYCLYL-  
4-PIPERIDINAMINES

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Background of the invention:

20 In U.S. Patent No. 4,219,559 there are described a number of  
1-substituted N-heterocyclyl-4-piperidinamines as compounds having  
useful anti-histaminic properties. The same reference also teaches the  
use of a number of N-heterocyclyl-4-piperidinamines having a piperidine  
moiety which is either unsubstituted in the 1-position or substituted  
25 with an alkyloxycarbonyl or phenylmethoxycarbonyl group, as useful  
intermediates. A number of these compounds are further described in more  
detail in J. Med. Chem. 1985, 28, pp. 1925-1933, 1934-1943 and 1943-1947.  
Furthermore, in J. Med. Chem. 1985, 28, 1934-1943 there are described  
the synthesis and anti-histaminic properties of the compound  
30 1-[(4-fluorophenyl)methyl]-4-(4-piperidinyl)-1H-benzimidazol-2-amine  
dihydrobromide. The latter compound is taught in "Astemizole: a New,  
Non-sedative, Long-acting H<sub>1</sub>-antagonist, Med. Publ. Found. Symp. Ser.  
84, 25-34 (1984)" to be an active metabolite of astemizole.

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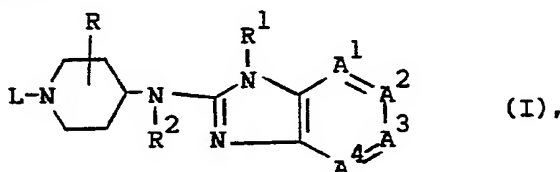
In U.S. Patent No. 4,556,660 and in the Published Eur. Pat. Appl. Nos. 145 037, 144 101 and 151 824 there are described further series of N-heterocyclyl-4-piperidinamines having a 1-substituted piperidine moiety as compounds having useful anti-histaminic and serotonin-antagonistic properties, while N-heterocyclic-4-piperidinamines being unsubstituted in the 1-position of the piperidine moiety are described as intermediates.

Finally, in the published Eur. Pat. Appl. No. 151,826 there are described a number of 4-(bicyclic heterocyclyl)methyl and -hetero-piperidines having useful anti-histaminic and serotonin-antagonistic properties.

The present invention concerns compositions containing the previously-mentioned N-heterocyclyl-4-piperidinamines bearing either a hydrogen atom, an alkyloxycarbonyl or phenylmethoxycarbonyl group in the 1-position of the piperidine moiety as active ingredients and methods of treating allergic diseases based on the use of the said compositions.

Description of the invention:

The present invention is concerned with anti-allergic compositions comprising one or more pharmaceutically acceptable inert carriers and as active ingredient an anti-allergic effective amount of at least one compound having the formula



the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

L is hydrogen, C<sub>1-6</sub> alkyloxycarbonyl or phenylmethoxycarbonyl;

A<sup>1</sup>=A<sup>2</sup>-A<sup>3</sup>=A<sup>4</sup> is a bivalent radical having the formula

-CH=CH-CH=CH- (a),

-N=CH-CH=CH- (b),

-CH=N-CH=CH- (c),

-CH=CH-N=CH- (d), or

-CH=CH-CH=N- (e),

wherein one or two hydrogen atoms in said radicals (a) - (e) may, each independently from each other, be replaced by halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy, trifluoromethyl or hydroxy;

R is a member selected from the group consisting of hydrogen and  
5 C<sub>1-6</sub> alkyl;

R<sup>1</sup> is a member selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, Ar<sup>1</sup> and C<sub>1-6</sub> alkyl substituted with one or two Ar<sup>1</sup> radicals;

R<sup>2</sup> is a member selected from the group consisting of hydrogen,  
10 C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, (C<sub>1-6</sub> alkyl)-CO-, (C<sub>1-6</sub> alkyloxy)-CO and Ar<sup>2</sup>-C<sub>1-6</sub> alkyl;

wherein Ar<sup>1</sup> is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy,  
15 nitro, cyano, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy, C<sub>1-6</sub> alkylthio, mercapto, amino, mono- and di(C<sub>1-6</sub> alkyl)amino, carboxyl, C<sub>1-6</sub> alkyloxycarbonyl and C<sub>1-6</sub> alkyl-CO-; thienyl; halothienyl; furanyl; C<sub>1-6</sub> alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted with C<sub>1-6</sub> alkyl; and  
20 wherein Ar<sup>2</sup> is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy, C<sub>1-6</sub> alkylthio, mercapto, amino, mono- and di(C<sub>1-6</sub> alkyl)amino, carboxyl, C<sub>1-6</sub> alkyloxycarbonyl and (C<sub>1-6</sub> alkyl)-CO.  
25

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term "C<sub>1-6</sub> alkyl" is meant to include straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl,  
30 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; "C<sub>1-10</sub> alkyl" is meant to include C<sub>1-6</sub> alkyl radicals, as defined hereinabove, and the higher homologs thereof having from 7 to 10 carbon atoms; the term "C<sub>3-6</sub> cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

35 Preferred compounds of formula (I) to be used as active ingredient

in the compositions of the present invention are those wherein  $A^1=A^2-A^3=A^4$  is a bivalent radical of formula (a) or (b) and  $R^1$  is  $C_{1-6}$  alkyl substituted with  $Ar^1$ .

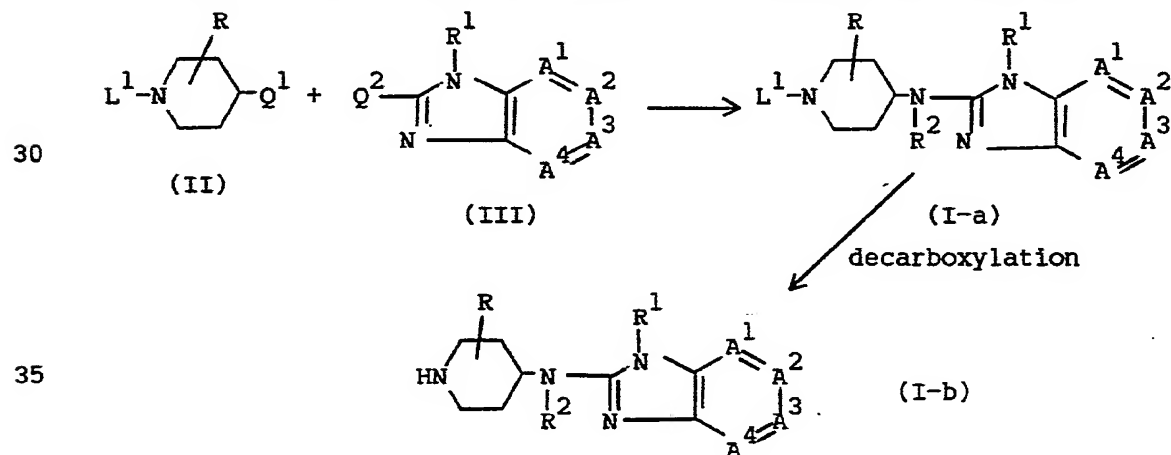
Particularly preferred compounds of formula (I) to be used as active ingredient in the compositions of the present invention are those wherein  $A^1=A^2-A^3=A^4$  is a bivalent radical of formula (a) or (b),  $R$  is hydrogen,  $R^2$  is hydrogen or  $C_{1-6}$  alkyl and  $R^1$  is  $C_{1-6}$  alkyl substituted with a member selected from the group consisting of phenyl being optionally substituted with up to two substituents independently selected from the group consisting of halo, hydroxy, and  $C_{1-6}$  alkyl; pyridyl; imidazolyl; thienyl; halothienyl; furanyl;  $C_{1-6}$  alkyl substituted furanyl; thiazolyl and pyrazinyl; whereby  $R^1$  being furanylmethyl or ( $C_{1-6}$  alkyl)furanylmethyl is especially preferred.

The most preferred compound of formula (I) to be used as active ingredient in the compositions of the present invention is 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine or a pharmaceutically acceptable acid addition salt thereof.

The compounds of formula (I) as well as their preparation are known and are described in, for example, U.S. Patent Nos. 4,219,559 and 4,556,660.

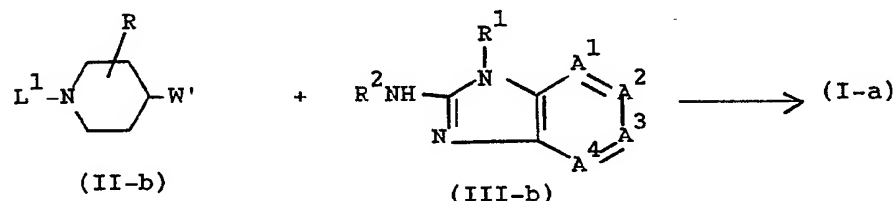
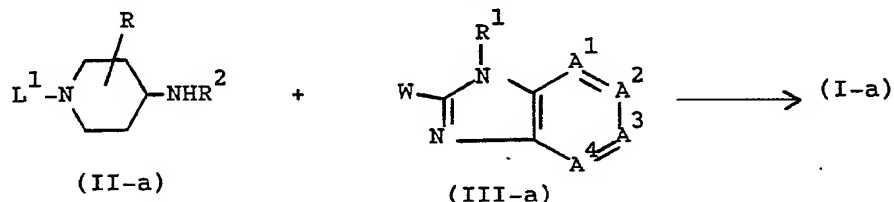
Beside the methods described in these patents, the compounds of formula (I) can also be prepared by a number of novel processes, said novel processes constituting a further aspect of the present invention.

The compounds of formula (I) can be prepared by reacting a piperidine derivative of formula (II) with a benzimidazole derivative of formula (III) optionally followed by a decarboxylation reaction.



In (II) and (I-a)  $L^1$  has the same meaning of L provided that it is not hydrogen, while  $Q^1$  and  $Q^2$  in (II), respectively (III) are selected so that during the reaction of (II) with (III) the  $-NR^2$ - moiety is formed connecting the piperidine and benzimidazole moiety.

For example  $Q^1$  may be a radical  $-NHR^2$  and  $Q^2$  a radical  $-W$  or inversely  $Q^1$  may be a radical  $-W'$  and  $Q^2$  a radical  $-NHR^2$

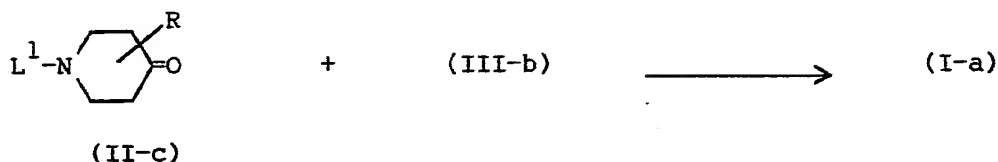


In (III-a) and (II-b) W and W' represent an appropriate leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy, whereas W may also be alkyloxy or alkylthio.

The reaction of (II-a) with (III-a) and of (II-b) with (III-b) are conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene, and the like; a lower alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; N,N-dimethylformamide (DMF); N,N-dimethylacetamide (DMA); nitrobenzene; dimethyl sulfoxide (DMSO); 1-methyl-2-pyrrolidinone; and the like. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. In some circumstances the addition of a iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the

rate of the reaction.

Or,  $Q^1$  may be an oxo radical and  $Q^2$  a radical  $-NHR^2$ .



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The reaction of (II-c) with (III-b) is conveniently carried out by treating a mixture of the reactants in a suitable reaction-inert organic solvent with an appropriate reductant. The reaction mixture may be stirred and/or heated in order to enhance the reaction rate. Preferably, the piperidone of formula (II-c) is first reacted with the benzimidazole-amine of formula (III-b) to form an enamine, which optionally may be isolated and further purified, and subsequently subjecting the said enamine to a reduction reaction. Suitable solvents are, for example, water;  $C_{1-6}$  alkanols, e.g. methanol, ethanol, 2-propanol and the like; cyclic ethers, e.g. 1,4-dioxane and the like; halogenated hydrocarbons, e.g. trichloromethane and the like; N,N-dimethylformamide; N,N-dimethylacetamide; dimethyl sulfoxide and the like; or a mixture of such solvents. Appropriate reductants are for example, metal or complex metal hydrides, e.g. sodium borohydride, lithium aluminiumhydride; or hydrogen, the latter being preferably used in the presence of a suitable catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene and the like.

The decarboxylation reaction of (I-a) to prepare the piperidine compounds of formula (I-b) may be performed by treating the starting compound of formula (I-a) with an acid or a base in a suitable solvent. As suitable acids or bases there may be cited hydrohalic acids, e.g. hydrochloric acid or hydrobromic acid, sulfuric, phosphoric and the like acids preferably employed as an aqueous solution or mixed with e.g. acetic acid. Suitable bases are the alkali metal hydroxides, hydrides or alkoxides in an aqueous or alcoholic medium.

In all of the foregoing and in the following preparations, the

reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

Conversely the salt form can be converted by treatment with alkali into the free base form.

The intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds.

From formula (I) it is evident that the compounds of this invention may have several asymmetric carbon atoms in their structure. Each of these chiral centers may be present in a R- and a S-configuration, this R- and S-notation being in correspondence with the rules described by R.S. Cahn, C. Ingold and V. Prelog in Angew. Chem., Int. Ed. Engl., 5, 385, 511 (1966).

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g., counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids.

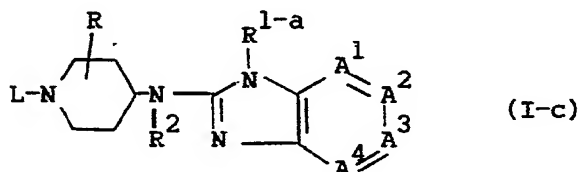
Pure stereochemically isomeric forms may also be derived from the

corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

It is evident that the cis and trans diastereomeric racemates may be further resolved into their optical isomers, cis(+), cis(-), trans(+) and trans(-) by the application of methodologies known to those skilled in the art.

Stereochemically isomeric forms of the compounds of formula (I) are naturally intended to be embraced within the scope of the invention.

An additional feature of the present invention comprises the fact that those compounds of formula (I) wherein  $R^1$  is  $C_{1-6}$  alkyl substituted with  $C_{1-6}$  alkyl-substituted furanyl and wherein said  $C_{1-6}$  alkyl-substituted furanyl is other than 5-methyl-2-furanyl, said compounds being represented by the formula



and the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof are novel compounds.

Preferred novel compounds are those compounds of formula (I-c) wherein  $R^{1-a}$  is  $C_{1-6}$  alkyl substituted with 3- or 4-( $C_{1-6}$  alkyl)-2-furanyl or with 2-( $C_{1-6}$  alkyl)-3-furanyl.

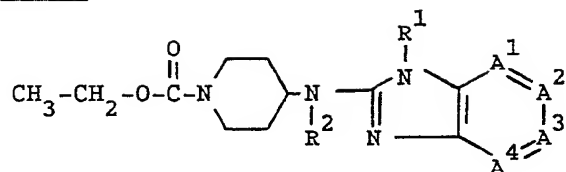
Particularly preferred novel compounds are those preferred novel compounds wherein  $R^{1-a}$  is methyl substituted with 3-( $C_{1-6}$  alkyl)-2-furanyl,  $R^2$  is hydrogen, R is hydrogen and  $A^1=A^2-A^3=A^4$  is  $CH=CH-CH=CH$  or  $N=CH-CH=CH$ .

Some of the compounds of formula (I) which can be used as active ingredient in the compositions and methods of treatment according to the present invention are listed in the following tables with the purpose of illustrating the invention and not to limiting it thereto.



Table I

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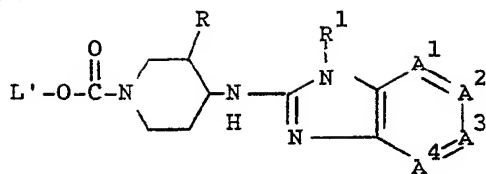
comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
1	H	H	-CH=CH-C(Cl)=CH-	base	234.1
2	H	H	-CH=CH-CH=CH-	base	-
3	H	H	-CH=CH-C(CH <sub>3</sub> )=CH-	base	-
4	CH <sub>3</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH-	base	142
5	CH <sub>3</sub>	H	or -CH=C(CH <sub>3</sub> )-CH=CH-	base	166.7
6	C <sub>2</sub> H <sub>5</sub>	H	-CH=CH-CH=CH-	base	-
7	C <sub>3</sub> H <sub>7</sub> -n	H	-CH=CH-CH=CH-	base	-
8	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
9	C <sub>5</sub> H <sub>11</sub> -n	H	-CH=CH-CH=CH-	base	-
10	C <sub>7</sub> H <sub>15</sub> -n	H	-CH=CH-CH=CH-	base	-
11	C <sub>4</sub> H <sub>9</sub> -n	H	-CH=CH-CH=CH-	base	-
12	C <sub>6</sub> H <sub>13</sub> -n	H	-CH=CH-CH=CH-	base	-
13	cyclopentyl	H	-CH=CH-CH=CH-	base	-
14	C <sub>3</sub> H <sub>7</sub> -i	H	-CH=CH-CH=CH-	base	-
15	H	CH <sub>3</sub>	-CH=CH-CH=CH-	base	-
16	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	CH <sub>3</sub>	-CH=CH-CH=CH-	HCl	258
17	4-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	202.6
18	2-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	213.4
19	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	177.7
20	4-Br-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
21	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	180.8
22	H	C <sub>4</sub> H <sub>9</sub> -n	-CH=CH-CH=CH-	base	225.9

	comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
5	23	2-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	176
	24	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH- or -CH=C(CH <sub>3</sub> )-CH=CH-	base	173.3
	25	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(CF <sub>3</sub> )=CH-	base	200
	26	H	H	-CH=CH-C(F)=CH-	base	227.5
10	27	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(Cl)=CH-	base	211.9
	28	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-N=CH-CH=CH-	base	148.6
	29	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH- or -CH=C(CH <sub>3</sub> )-CH=CH-	base	179.3
	30	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-N=CH-CH=CH-	base	134.4
15	31	H	H	-N=CH-CH=CH-	base	216.1
	32	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(Cl)=CH-	base	215.8
	33	C <sub>6</sub> H <sub>5</sub>	H	-CH=CH-CH=CH-	base	137
	34	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(F)=CH- or -CH=C(F)-CH=CH-	base	182.5
20	35	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(F)=CH- or -CH=C(F)-CH=CH-	base	184
	36	4-F-C <sub>6</sub> H <sub>5</sub>	H	-CH=CH-CH=CH-	base	153
	37	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	
	38	2-CH <sub>3</sub> , 4-F-C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	
25	39	C <sub>6</sub> H <sub>5</sub> -C <sub>2</sub> H <sub>4</sub>	H	-CH=CH-CH=CH-	H <sub>2</sub> O	71.2
	40	4-F-C <sub>6</sub> H <sub>4</sub> -C <sub>2</sub> H <sub>4</sub>	H	-CH=CH-CH=CH-	ethanolate (1:1)	110.2
	41	3-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	184.6
	42	H	H	-CH=CH-C(OCH <sub>3</sub> )=CH-	base	-
30	43	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(OCH <sub>3</sub> )=CH- or -CH=C(OCH <sub>3</sub> )-CH=CH-	base	169.8
	44	2-pyridinyl- methyl	H	-CH=CH-CH=CH-	base	161.5

comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
5	45	H	-CH=CH-N=CH-	2HCl. 1/2H <sub>2</sub> O	206.3- 209.1
	46	3-pyridinyl- methyl	-CH=CH-CH=CH-	base	191.4
	47	5-CH <sub>3</sub> -4-imi- dazolylmethyl	-CH=CH-CH=CH-	2HCl	233.7
	48	2-pyrazinyl- methyl	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	178.5- 179.3
	49	2-furanyl- methyl	-CH=CH-CH=CH-	base	135.8
10	50	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=CH-CH=N-	base	212.5
	51	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=CH-N=CH-	2HCl.H <sub>2</sub> O	-
	52	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=N-CH=CH-	2HCl.H <sub>2</sub> O	168.6
	53	2-pyridinyl- methyl	-N=CH-CH=CH-	base	141.3
	54	H	-CH=C(F)-C(F)=CH-	base	234.9
15	55	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=C(F)-C(F)=CH-	base	182.3
	56	2-furanyl- methyl	-N=CH-CH=CH-	base	149.2
	57	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=CH-C(OCH <sub>3</sub> )=CH-	base	-
	58	2-thienyl- methyl	-CH=CH-CH=CH-	base	142.7
	59	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=C(OCH <sub>3</sub> )-CH=CH-	base	-
20	60	3-furanyl- methyl	-CH=CH-CH=CH-	base	150.7
	61	5-methyl-2- furanylmethyl	-CH=CH-CH=CH-	1/2H <sub>2</sub> O	150.1
	62	2-thienyl- methyl	-N=CH-CH=CH-	base	-
	63	4-thiazolyl methyl	-CH=CH-CH=CH-	base	156.2
	64	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	157.1
25	65	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	-
	66	H	-CH=CH-CH=CH-	base	-
	67	3-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	-
	68	3,4-(CH <sub>3</sub> ) <sub>2</sub> - C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	-

comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
5	69 2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
	70 3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
	71 2-Br, 4-F- C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
10	72 2-I-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
	73 4-CH <sub>3</sub> OC(O)- C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	151
	74 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH-	base	202
15	75 2,4-Cl <sub>2</sub> - C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
	76 2,6-F <sub>2</sub> - C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	140
	77 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	oil
20	78 cyclohexyl	H	-CH=CH-CH=CH-	base	-
	79 5-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	-
	80 3-furanylmethyl	H	-N=CH-CH=CH-	base	174.5
25	81 2-methyl-3-furanylmethyl	H	-N=CH-CH=CH-	base	153.7
	82 5-ethyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	111.1
	83 2-methyl-3-furanylmethyl	H	-CH=CH-CH=CH-	base	150.4
30	84 5-methyl-2-furanylmethyl	H	-CH=CH-N=CH-	base	155.2
	85 3-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	-
	86 5-methyl-2-furanylmethyl	H	-CH=N-CH=CH-	base	-
30	87 5-isopropyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	-
	88 4-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	-

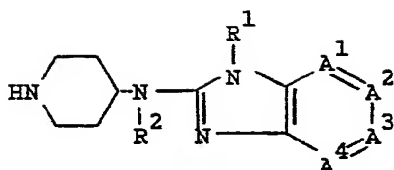
Table II



comp. no.	L'	R <sup>1</sup>	R	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
89	CH <sub>3</sub>	H	CH <sub>3</sub>	-CH=CH-CH=CH-	base	155
90	CH <sub>3</sub>	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	CH <sub>3</sub>	-CH=CH-CH=CH-	base	172.5
91	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-N=CH-CH=CH-	base	130
92*	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	CH <sub>3</sub>	-CH=CH-CH=CH-	base	191

\* : cis+trans isomer

Table III



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comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
93	H	H	-CH=CH-CH(Cl)=CH-	2HBr	-
94	H	H	-CH=CH-CH=CH-	2HBr	-
95	CH <sub>3</sub>	H	-CH=CH-C(CH <sub>3</sub> )-CH- or -CH=C(CH <sub>3</sub> )-CH=CH-	2HBr	-
96	H	H	-CH=C(CH <sub>3</sub> )-C=CH-	2HBr	-
97	CH <sub>3</sub>	H	-CH=CH-CH=CH-	2HBr	-
98	C <sub>2</sub> H <sub>5</sub>	H	-CH=CH-CH=CH-	2HBr.	334-
99	C <sub>3</sub> H <sub>7</sub> -n	H	-CH=CH-CH=CH-	1/2H <sub>2</sub> O	338
100	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
101	C <sub>5</sub> H <sub>11</sub> -n	H	-CH=CH-CH=CH-	base	-
102	C <sub>7</sub> H <sub>15</sub> -n	H	-CH=CH-CH=CH-	base	-
103	C <sub>4</sub> H <sub>9</sub> -n	H	-CH=CH-CH=CH-	base	-
104	C <sub>6</sub> H <sub>13</sub> -n	H	-CH=CH-CH=CH-	base	-
105	cyclopentyl	H	-CH=CH-CH=CH-	base	-
106	C <sub>3</sub> H <sub>7</sub> -i	H	-CH=CH-CH=CH-	base	-
107	H	CH <sub>3</sub>	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	-
108	2-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	-
109	4-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	-
110	4-Br-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	>300
111	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
112	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	290.2
113	H	C <sub>4</sub> H <sub>9</sub> -n	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	223.1
114	2-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
115	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(CF <sub>3</sub> )=CH-	2HBr	-

comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
5	116 C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(Cl)=CH-	2HBr	>260
	117 C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-N=CH-CH=CH-	2HCl.H <sub>2</sub> O	298.1
	118 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(Cl)=CH-	2HBr	>260
	119 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH- or -CH=C(CH <sub>3</sub> )-CH=CH-	2HBr	-
10	120 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(F)=CH- or -CH=C(F)-CH=CH-	2HBr	285.6
	121 C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH- or -CH=C(CH <sub>3</sub> )-CH=CH-	2HBr	-
	122 C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	H	-CH=CH-C(F)=CH- or -CH=C(F)-CH=CH-	2HBr	>260
15	123 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-N=CH-CH=CH-	2HCl.H <sub>2</sub> O	269.7
	124 C <sub>6</sub> H <sub>5</sub>	H	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	>300
	125 4-F-C <sub>6</sub> H <sub>5</sub> -	H	-CH=CH-CH=CH-	2HBr	>300
	126 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr.H <sub>2</sub> O	-
20	127 2-CH <sub>3</sub> , 4-F-C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
	128 C <sub>6</sub> H <sub>5</sub> -C <sub>2</sub> H <sub>4</sub>	H	-CH=CH-CH=CH-	base	181.8
	129 3-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	218.4
25	130 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(OH)-CH- or -CH=C(OH)-CH=CH-	2HBr	-
	131 2-pyridinyl-methyl	H	-CH=CH-CH=CH-	3HBr	295.9
	132 3-pyridinyl-methyl	H	-CH=CH-CH=CH-	3HBr	>260
30	133 5-CH <sub>3</sub> -4-imidazolylmethyl	H	-CH=CH-CH=CH-	2HBr	272.1
	134 2-pyrazinyl-methyl	H	-CH=CH-CH=CH-	3HBr	-
	135 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=N-	2HBr	>300.6
35	136 2-furanyl-methyl	H	-CH=CH-CH=CH-	base	211.0
	137 4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	215.5

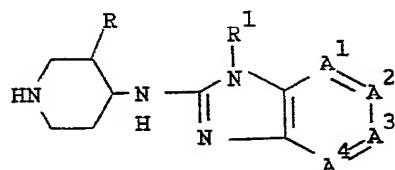
	comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
5	138	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-N=CH-	2HBr	279.4
	139	2-pyridinyl- methyl	H	-N=CH-CH=CH-	3HBr	265.5
	140	2-furanyl- methyl	H	-N=CH-CH=CH-	base	159.0
	141	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=N-CH=CH-	2HBr.H <sub>2</sub> O	291.6
	142	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=C(F)-C(F)=CH-	2HBr	210.6
10	143	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(OH)=CH-	2HBr	-
	144	2-thienyl- methyl	H	-CH=CH-CH=CH-	base	-
	145	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=C(OH)-CH=CH-	2HBr	-
	146	3-furanyl- methyl	H	-CH=CH-CH=CH-	base	-
	147	5-methyl-2- furanylmethyl	H	-CH=CH-CH=CH-	base	-
15	148	2-thienyl- methyl	H	-N=CH-CH=CH-	base	189.6 193.5
	149	4-thiazolyl methyl	H	-CH=CH-CH=CH-	2HBr.2H <sub>2</sub> O	223.5
	150	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	base	178.1
	151	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(OCH <sub>3</sub> )=CH-	base	-
	152	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	CH <sub>3</sub>	-CH=CH-CH=CH-	2HCl.H <sub>2</sub> O	222.2
20	153	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=C(OCH <sub>3</sub> )-CH=CH-	base	-
	154	H	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	-
	155	3-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	262.2
	156	3,4-(CH <sub>3</sub> ) <sub>2</sub> - C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
	157	2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
25	158	3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
	159	2-Br,4-F- C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	-
	160	2-I-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr.2H <sub>2</sub> O	265.2
	161	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	H	-CH=CH-C(CH <sub>3</sub> )=CH-	base	-



	comp. no.	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
5	162	2,4-Cl <sub>2</sub> - C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	225.6
	163	2,6-F <sub>2</sub> - C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub>	H	-CH=CH-CH=CH-	2HBr	295.5
	164	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	-CH=CH-CH=CH-	base	-
	165	cyclohexyl	H	-CH=CH-CH=CH-	base	180
	166	5-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	119.8
10	167	3-furanylmethyl	H	-N=CH-CH=CH-	base	145
	168	2-furanylmethyl	H	-N=CH-CH=CH-	(Z)-2-butenedioate (1:2)	170.0
	169	2-furanylmethyl	H	-N=CH-CH=CH-	2HCl.1/2H <sub>2</sub> O	200.9
15	170	2-furanylmethyl	H	-N=CH-CH=CH-	*	131.5
	171	3-furanylmethyl	H	-N=CH-CH=CH-	2HCl.1/2H <sub>2</sub> O	278.7
	172	H	H	-N=CH-CH=CH-	2HBr	295.1
	173	2-methyl-3-furanylmethyl	H	-N=CH-CH=CH-	base	164.7
20	174	5-ethyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	106.1
	175	5-methyl-2-furanylmethyl	H	-CH=CH-N=CH-	base	185.6
	176	2-methyl-3-furanylmethyl	H	-CH=CH-CH=CH-	base	168.0
	177	3-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	base	160.3
25	178	5-methyl-2-furanylmethyl	H	-CH=N-CH=CH-	1/2H <sub>2</sub> O	146.2
	179	5-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	2HCl.1/2H <sub>2</sub> O	204.1
	180	5-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	2HNO <sub>3</sub>	170.5
30	181	5-methyl-2-furanylmethyl	H	-N=CH-CH=CH-	(Z)-2-butenedioate (1:2)	154.5
	182	5-isopropyl-2-furanylmethyl	H	-N=CH-CH=CH-		
35	183	4-methyl-2-furanylmethyl	H	-N=CH-CH=CH-		

\* : (+)-[R-(R\*,R\*)]-2,3-dihydroxybutanedioate (2:3)

Table IV



comp. no.	R <sup>1</sup>	R	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Salt/base	mp. (°C)
184	4-F-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	CH <sub>3</sub>	-CH=CH-CH=CH-	2HBr	-
185	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	CH <sub>3</sub>	-CH=CH-CH=CH-	2HBr·H <sub>2</sub> O	250.2

The use of the compounds of formula (I), the pharmaceutically acceptable acid-addition salts and possible stereochemically isomeric forms thereof in the compositions of the present invention is based on their useful pharmacological properties. More particularly, they are  
5 active as anti-histaminics which activity is clearly evidenced by the results obtained in the "Protection of Rats from Compound 48/80-induced lethality"-test. In addition thereto, they are also devoid of sedating effects which is an undesirable side-effect often encountered with anti-histaminics. Apart from their anti-histaminic properties they also  
10 show serotonin-antagonism.

Furthermore, the compounds of formula (I), the pharmaceutically acceptable acid-addition salts and stereochemically isomeric forms thereof are particularly attractive due to their favourable pharmacokinetical profile. On the one hand they show a rapid onset so  
15 that their anti-histaminic effects are almost instantaneously present. On the other hand they possess an attractive duration of effect, i.e., while being not too short, thus avoiding the necessity of frequent administrations, said duration is not too long either. Hence, the dose regimen can suitably be adapted to the evolution of the symptoms.

20 To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for  
25 administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water,  
30 glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets  
35 and capsules represent the most advantageous oral dosage unit form, in

which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may  
5 be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier  
10 optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for  
15 preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions. It  
20 is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined  
25 quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoon-fuls and  
30 the like, and segregated multiples thereof.

In a further aspect of the present invention there is provided a method of treating allergic diseases in warm-blooded animals suffering from said allergic diseases, which method comprises the administration  
35 to said warm-blooded animals of an effective anti-allergic amount of a compound of formula (I) a pharmaceutically acceptable acid-addition salt

or possible stereochemically isomeric form thereof. Preferably said effective amount of the active ingredient is administered as a composition as described hereinabove. Those of skill in the pertinent art could easily determine the effective anti-allergic amount from the test results presented here. In general it is contemplated that an effective amount would be from 0.001 mg/kg to 100 mg/kg body weight, and more preferably from 0.01 mg/kg to 1 mg/kg body weight.

#### EXAMPLES

##### A) Preparation of Intermediates

###### Example 1

A mixture of 47.5 parts of  $N^2$ -(2-furanylmethyl)-2,3-pyridine-diamine, 36.5 parts of methyl ( $\alpha$ -imino- $\alpha$ -methoxymethyl)-carbamate, 34.5 parts of acetic acid and 450 parts of methylbenzene was stirred and heated for 16 hours at 65-68°C. The reaction mixture was evaporated. 140 Parts of potassium hydroxide, 50 parts of water and 400 parts of 2-propanol were added to the residue and stirring was continued for 16 hours at reflux. The reaction mixture was concentrated to 1/4 of its volume. 500 Parts of water were added and 2-propanol was distilled off azeotropically. After stirring for 1 hour at room temperature, the product was filtered off, washed successively twice with 20 parts of water and three times with 12 parts of 2-propanone and crystallized from 1,2-dichloroethane. The product was filtered off and dried in vacuo at 50°C, yielding 27.3 parts (51.0%) of 3-(2-furanylmethyl)-3H-imidazo-[4,5-b]pyridin-2-amine; mp. 193.3°C.

##### B) Preparation of Final Compounds

###### Example 2

A mixture of 22.2 parts of ethyl 4-oxo-1-piperidinecarboxylate, 21.4 parts of 3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine, 360 parts of methylbenzene and 0.1 parts of 4-methylbenzenesulfonic acid was stirred for 4 days at reflux temperature using a water separator. After cooling to 50°C, 64 parts of ethanol were added and 3.8 parts of sodium

tetrahydroborate were added portionwise to the reaction mixture. Upon completion, stirring was continued for 2 hours at 50°C. After cooling, the mixture was decomposed with 3.5 parts of acetic acid. Water was added to the mixture while stirring and the layers were separated. The aqueous layer was extracted with methylbenzene. The combined methylbenzene layers were dried, filtered and evaporated, yielding ethyl 4-[[3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidine-carboxylate as an oily residue (compound 56).

#### Example 3

A mixture of ethyl 4-[[3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinecarboxylate, 50 parts of potassium hydroxide, 400 parts of 2-propanol and 20 drops of water was stirred and refluxed for about 5 hours. The reaction mixture was evaporated and water was added to the residue. The product was extracted twice with 4-methyl-2-pentanone. The combined extracts were dried, filtered and evaporated. The solid residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 34 parts (85%) of 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 159.0°C (compound 140)

#### Example 4

A mixture of 9.8 parts of ethyl 4-amino-1-piperidinecarboxylate and 15 parts of 2-chloro-1-(4-fluorophenylmethyl)-1H-benzimidazole was heated to 120°C. The mixture was stirred at 120°C during 43 hours. After cooling, 100 parts of trichloromethane were added and the whole was thoroughly stirred. The mixture was washed with water. The aqueous layer was separated and the organic mixture was filtered and evaporated. The collected solid material was dissolved in 100 parts of water and subsequently 100 parts of 20% sodium hydroxide solution were added. The precipitate was filtered and dried in vacuo at 50°C, yielding 12.1 parts (40.5%) of ethyl 4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinecarboxylate; mp. 181°C (compound 21).

#### Example 5

A mixture of 3.2 parts of ethyl 4-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate and 300 parts of

hydrobromic acid solution 48% was stirred and refluxed for 1 hour. The reaction mixture was evaporated and the residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 3.3 parts (82%) of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide; mp. 290.2°C (compound 112)

All other compounds listed in Tables I to IV can be obtained by analogous methods of preparation.

10 B) Pharmacological Examples

The useful anti-histaminic properties of the compounds of formula (I) which can be used as the active ingredient in the formulations according to the present invention can be demonstrated by the following test procedure.

15 Example 6

Protection of rats from compound 48/80-induced lethality.

Compound 48/80, a mixture of oligomers obtained by condensation of 4-methoxy-N-methylbenzeneethanamine and formaldehyde has been described as a potent histamine releasing agent (Int. Arch. Allergy, 13, 336 (1958)). The protection from compound 48/80-induced lethal circulatory collapse appears to be a simple way of evaluating quantitatively the antihistaminic activity of test compounds. Male rats of an inbred Wistar strain, weighing 240-260 g were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temp. =  $21 \pm 1^\circ\text{C}$ , relative humidity =  $65 \pm 5\%$ ).

The rats were treated subcutaneously or orally with a test compound or with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 ml/100 g of body weight). In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80, not more than 2.8% of the animals survived after 4 hours. Survival after 4 hours is therefore considered to be a safe criterion of a protective effect of drug administration. The  $\text{ED}_{50}$ -values of the compounds of formula (I) are listed in table 1. Said  $\text{ED}_{50}$ -values are the values in mg/kg body weight at which the

tested compounds protect 50% of the tested animals against compound 48/80-induced lethality.

Table I

No.	compound 48/80 lethality test in rats-ED <sub>50</sub> in mg/kg body weight
112	0.056
123	0.08
135	0.01
140	0.08
166	0.04

C) Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic administration to animal and human subjects in accordance with the present invention. These examples are given to illustrate and not to limit the scope of the present invention.

Example 7 : ORAL DROPS

500 g of 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo-[4,5-b]pyridin-2-amine was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60-80°C. After cooling to 30-40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg of the 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine per ml. The resulting solution was filled into suitable containers.



Example 8 : ORAL SOLUTION

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 20 mg of 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 9 : CAPSULES

20 g of 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine, 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelating capsules, comprising each 20 mg of 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine.

Example 10: FILM-COATED TABLETSPreparation of tablet core

A mixture of 100 g of 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine, 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol

there was added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former  
5 and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole was homogenated.

The tablet cores were coated with the thus obtained mixture in a coating apparatus.

10 Example 11: INJECTABLE SOLUTION

1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 propylene glycol and 4 g of 3-(2-furanylmethyl)-N-(4-piperidinyl)-  
15 3H-imidazo[4,5-b]pyridin-2-amine. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

20 Example 12: SUPPOSITORIES

3 g 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant and triglycerides q.s. ad 300 g were molten together. The  
25 latter mixture was mixed well with the former solution. The thus obtained mixture was poured onto moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg of 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine.

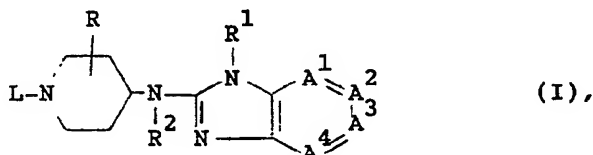
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CLAIMS

- 1 1. A pharmaceutical composition comprising a suitable
- 2 pharmaceutical carrier and as active ingredient a therapeutically
- 3 effective amount of a chemical compound having the formula



- 4 a pharmaceutically acceptable acid addition salt or a possible
- 5 stereochemically isomeric form thereof, wherein:
- 6 L is hydrogen, C<sub>1-6</sub> alkyloxycarbonyl or phenylmethoxycarbonyl;
- 7 A<sup>1</sup>=A<sup>2</sup>-A<sup>3</sup>=A<sup>4</sup> is a bivalent radical having the formula
- 8 -CH=CH-CH=CH- (a),
- 9 -N=CH-CH=CH- (b),
- 10 -CH=N-CH=CH- (c),
- 11 -CH=CH-N=CH- (d), or
- 12 -CH=CH-CH=N- (e),
- 13 wherein one or two hydrogen atoms in said radicals (a) - (e) may, each
- 14 independently from each other, be replaced by halo, C<sub>1-6</sub> alkyl,
- 15 C<sub>1-6</sub> alkyloxy, trifluoromethyl or hydroxy;
- 16 R is a member selected from the group consisting of hydrogen and
- 17 C<sub>1-6</sub> alkyl;
- 18 R<sup>1</sup> is a member selected from the group consisting of hydrogen,
- 19 C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, Ar<sup>1</sup> and C<sub>1-6</sub> alkyl substituted
- 20 with one or two Ar<sup>1</sup> radicals;
- 21 R<sup>2</sup> is a member selected from the group consisting of hydrogen,
- 22 C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, (C<sub>1-6</sub> alkyl)-CO-, (C<sub>1-6</sub> alkyloxy)-CO
- 23 and Ar<sup>2</sup>-C<sub>1-6</sub> alkyl;
- 24 wherein Ar<sup>1</sup> is a member selected from the group consisting of
- 25 phenyl, being optionally substituted with up to three substituents
- 26 each independently selected from the group consisting of halo,
- 27 hydroxy, nitro, cyano, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy,
- 28 C<sub>1-6</sub> alkylthio, mercapto, amino, mono- and di(C<sub>1-6</sub> alkyl)amino,
- 29 carboxyl, C<sub>1-6</sub> alkyloxycarbonyl and C<sub>1-6</sub> alkyl-CO-; thienyl;
- 30 halothienyl; furanyl; C<sub>1-6</sub> alkyl substituted furanyl; pyridinyl;

31 pyrazinyl; thiazolyl and imidazolyl optionally substituted with C<sub>1-6</sub>  
32 alkyl; and wherein Ar<sup>2</sup> is a member selected from the group  
33 consisting of phenyl being optionally substituted with up to three  
34 substituents each independently selected from the group consisting of  
35 halo, hydroxy, nitro, cyano, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub>  
36 alkyloxy, C<sub>1-6</sub> alkylthio, mercapto, amino, mono- and di(C<sub>1-6</sub>  
37 alkyl)amino, carboxyl, C<sub>1-6</sub> alkyloxycarbonyl and (C<sub>1-6</sub> alkyl)-CO.

1           2. An anti-allergic pharmaceutical composition comprising a  
2 suitable pharmaceutical carrier and as active ingredient an  
3 effective anti-allergic amount of a compound of formula (I) as  
4 defined in claim 1.

1           3. A composition according to any of claims 1 or 2 wherein  
2 A<sup>1</sup>=A<sup>2</sup>-A<sup>3</sup>=A<sup>4</sup> is a bivalent radical of formula (a) or (b) and R<sup>1</sup> is  
3 C<sub>1-6</sub> alkyl substituted with Ar<sup>1</sup>.

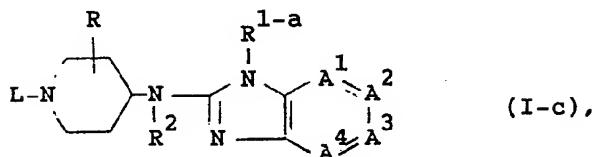
1           4. A composition according to claim 3 wherein R is hydrogen,  
2 R<sup>2</sup> is hydrogen or C<sub>1-6</sub> alkyl and Ar<sup>1</sup> is phenyl being optionally  
3 substituted with up to two substituents independently selected from  
4 the group consisting of halo, hydroxy, and C<sub>1-6</sub> alkyl; pyridyl;  
5 imidazolyl; thienyl; halothienyl; furanyl; C<sub>1-6</sub> alkyl substituted  
6 furanyl; thiazolyl and pyrazinyl.

1           5. A composition according to claim 4 wherein R<sup>1</sup> is furanylmethyl  
2 or (C<sub>1-6</sub> alkyl)furanylmethyl.

1           6. A composition according to claim 5 wherein the compound is  
2 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]-  
3 pyridin-2-amine.

1           7. A method of preparing a pharmaceutical composition as claimed  
2 in any of claims 1 to 7, characterized in that a therapeutically  
3 effective amount of a compound of formula (I) as defined in any of said  
4 claims 1 to 7 is intimately mixed with suitable pharmaceutical carriers.

1 8. A chemical compound having the formula



2 a pharmaceutically acceptable acid addition salt or a possible  
3 stereochemically isomeric form thereof, wherein:

4 L is hydrogen, C<sub>1-6</sub> alkyloxycarbonyl or phenylmethoxycarbonyl;

5 A<sup>1</sup>=A<sup>2</sup>-A<sup>3</sup>=A<sup>4</sup> is a bivalent radical having the formula

6 -CH=CH-CH=CH- (a),

7 -N=CH-CH=CH- (b),

8 -CH=N-CH=CH- (c),

9 -CH=CH-N=CH- (d), or

10 -CH=CH-CH=N- (e),

11 wherein one or two hydrogen atoms in said radicals (a) - (e) may,

12 each independently from each other, be replaced by halo, C<sub>1-6</sub>

13 alkyl, C<sub>1-6</sub> alkyloxy, trifluoromethyl or hydroxy;

14 R is a member selected from the group consisting of hydrogen and  
15 C<sub>1-6</sub> alkyl;

16 R<sup>1-a</sup> is C<sub>1-6</sub> alkyl substituted with C<sub>1-6</sub> alkyl-substituted  
17 furanyl and wherein said C<sub>1-6</sub> alkyl-substituted furanyl is other  
18 than 5-methyl-2-furanyl;

19 R<sup>2</sup> is a member selected from the group consisting of hydrogen,  
20 C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, (C<sub>1-6</sub> alkyl)-CO-, (C<sub>1-6</sub> alkyloxy)-CO  
21 and Ar<sup>2</sup>-C<sub>1-6</sub> alkyl;

22 wherein Ar<sup>2</sup> is a member selected from the group consisting of  
23 phenyl being optionally substituted with up to three substituents  
24 each independently selected from the group consisting of halo,  
25 hydroxy, nitro, cyano, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub>  
26 alkyloxy, C<sub>1-6</sub> alkylthio, mercapto, amino, mono- and di(C<sub>1-6</sub>  
27 alkyl)amino, carboxyl, C<sub>1-6</sub> alkyloxycarbonyl and (C<sub>1-6</sub> alkyl)-CO.

1 9. A compound according to claim 8 wherein R<sup>1-a</sup> is C<sub>1-6</sub> alkyl  
2 substituted with 3- or 4-(C<sub>1-6</sub> alkyl)-2-furanyl or with 2-(C<sub>1-6</sub> alkyl)-  
3 3-furanyl.

1 10. A compound according to claim 9 wherein  $R^{1-a}$  is methyl  
 2 substituted with 3-(C<sub>1-6</sub> alkyl)-2-furanyl,  $R^2$  is hydrogen, R is  
 3 hydrogen and  $A^1=A^2-A^3=A^4$  is CH=CH-CH=CH or N=CH-CH=CH.

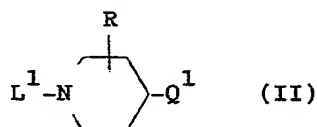
1 11. A chemical compound of formula (I) as defined in any of  
 2 claims 1 to 7 for use as a medicine.

1 12. A chemical compound of formula (I) as defined in any of  
 2 claims 1 to 7 for use as an anti-allergic medicine.

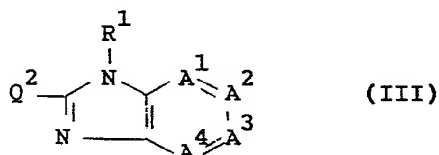
1 13. A compound as claimed in any one of claims 8 to 10 for use as  
 2 a medicine.

1 14. A compound as claimed in any one of claims 8 to 10 for use as  
 2 an anti-allergic medicine.

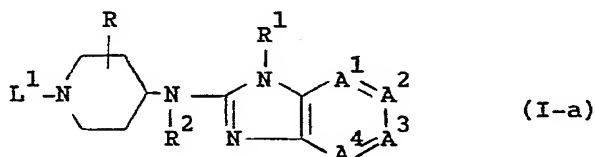
1 15. A process for preparing a chemical compound of formula (I) as  
 2 defined in claim 1, characterized by  
 3 reacting a piperidine of formula



4 wherein  $L^1$  is as L provided that it is not hydrogen, with a  
 5 benzimidazole of formula



6 in a reaction-inert solvent and, if desired, subsequently decar-  
 7 boxylating the group  $L^1$  in the thus obtained compound of formula



8 wherein in (II) and (III) either  
9  $Q^1$  is  $-NHR^2$  and  $Q^2$  is  $-W$ , or  
10  $Q^1$  is  $-W$  and  $Q^2$  is  $-NHR^2$ , or  
11  $Q^1$  is  $=O$  and  $Q^2$  is  $-NHR^2$ ;  
12 said  $W$  being a reactive leaving group;  
13 and, if further desired, converting the compounds of formula (I)  
14 into a salt form by treatment with an appropriate acid; or  
15 conversely, converting the salt into the free base with alkali;  
16 and/or preparing stereochemically isomeric forms thereof.

1 16. A process according to claim 15 wherein  $R^1$  is  $R^{1-a}$  as  
2 defined in claim 8.

(19)



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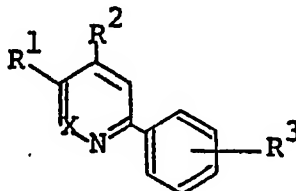
**3, Doshomachi 4-chome Higashi-ku  
Osaka-shi Osaka 541(JP)**

(72) Inventor: **Takasugi, Hisashi**  
**No. 14-33, Hamaguchinishi 1-chome  
Suminoe-ku Osaka 559(JP)**

Inventor: **Kuno, Atsushi**  
**No. 5-C-309, Hanjo 3-chome  
Mino Osaka, 562(JP)**

Inventor: **Sakai, Hiroyoshi**  
**No. 28-134, Kowada-Hirao  
Uji Kyoto, 611(JP)**  
Inventor: **Sugiyama, Yoshie**  
**No. 2-1, Nakayama-Sakuradai 5-chome  
Takarazuka Hyogo 665(JP)**

Inventor: **Takaya, Takao**  
**No. 5-87, Suimeidai 1-chome  
Kawanishi-shi Hyogo 666-01(JP)**

(74) Representative: **Pennant, Pyers et al**  
**Stevens, Hewlett & Perkins 5 Quality Court  
Chancery Lane  
London, WC2A 1HZ(GB)**(54) **N-containing heterocyclic compounds, processes for the preparation thereof and composition comprising the same.**(57) **An N-containing heterocyclic compound of the formula:**



wherein R<sup>1</sup> is lower alkyl optionally substituted with hydroxy, halogen or a heterocyclic group, carboxy, esterified carboxy, carbamoyl optionally substituted with heterocyclic(lower)alkyl or lower alkylamino-(lower)alkyl, N-containing heterocycliccarbonyl optionally substituted with lower alkyl, or ureido optionally substituted with lower alkylamino(lower)alkyl, and

R<sup>3</sup> is hydrogen or halogen;

R<sup>2</sup> is phenyl substituted with nitro, and

X is =N- or



in which R<sup>4</sup> is lower alkyl or halo (lower) alkyl, or is taken together with R<sup>1</sup> to form an N-containing heterocyclic group optionally substituted with oxo and lower alkylamino(lower)alkyl; or

R<sup>2</sup> is lower alkyl, and

X is



in which R<sup>4</sup> is phenyl substituted with nitro;

and a pharmaceutically acceptable salt thereof, processes for the preparation thereof and composition comprising the same.



EP 86 30 9657

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
	No relevant documents have been disclosed -----		C 07 D 213/80 C 07 D 237/24 C 07 D 213/82 C 07 D 213/30 C 07 D 237/08 C 07 D 213/26 C 07 D 213/36 C 07 D 471/04 A 61 K 31/44 A 61 K 31/50 // (C 07 D 471/04 C 07 D 221:00 C 07 D 209:00 )
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 211/00 C 07 D 211/00 C 07 D 237/00 C 07 D 471/00
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 22-11-1988	Examiner LEONARD
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : Intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document			

(19)



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Applicant: **ELI LILLY AND COMPANY, 307, East McCarty Street, Indianapolis Indiana 46285 (US)**

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(72)

Inventor: **Katner, Allen Samuel, 219 W. 81st Street, Indianapolis Indiana 46260 (US)**

(64)

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(74)

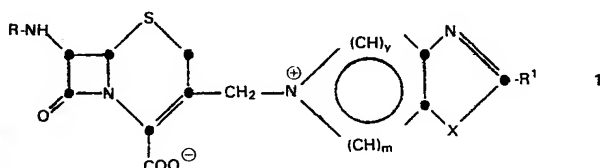
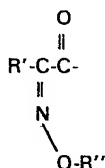
Representative: **Hudson, Christopher Mark et al, Erl Wood Manor, Windlesham Surrey GU20 6PH (GB)**

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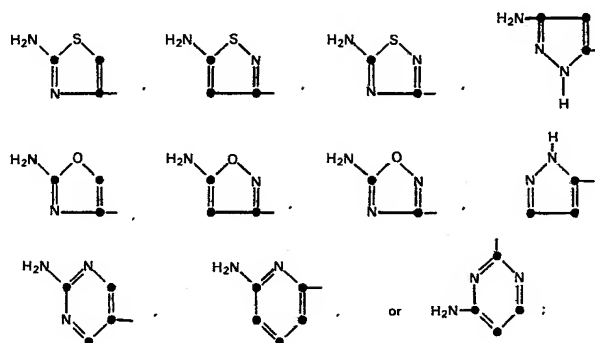
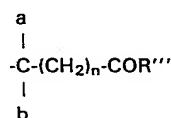
Improvements on or relating to 3-bicyclicpyridinium-methyl cephalosporins.

(57)

Cephalosporin compounds substituted in the 7-position by a 2-(5- or 6-membered heterocyclic)-2-oximinoacetyl amino group and of the formula

in which R is hydrogen, formyl,  $\alpha$ -aminoadipoyl, protected  $\alpha$ -aminoadipoyl, or an acyl group of the formula

in which R' is a 5- or 6-membered heterocyclic ring of the formulae

R'' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:

in which n is 0-3; a and b when taken separately are, independently, hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, and when taken together with the carbon to which they are bonded form a C<sub>3</sub>-C<sub>7</sub> carbocyclic ring; R''' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, or OR<sup>o</sup>, in which R<sup>o</sup> is indanyl, phthalidyl, or an acyloxymethyl group of the formula -CH<sub>2</sub>-O-C(O)-R<sub>2</sub> in which R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or COOR<sup>o</sup> is a protected carboxy group; or R'' is an N-substituted carbamoyl group of the formula



in which R'''' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

Y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof.

TitleIMPROVEMENTS ON OR RELATING TO  
3-BICYCLICPYRIDINIUM-METHYL CEPHALOSPORINS

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This invention relates to novel cephalosporin antibiotics which structurally contain a 7-[2-(amino-substituted-5- or 6-membered heterocyclic ring)-2-oxy-iminoacetyl-amino] side chain and a bicyclic pyridinium methyl group in the 3-position of the cephalosporin nucleus.

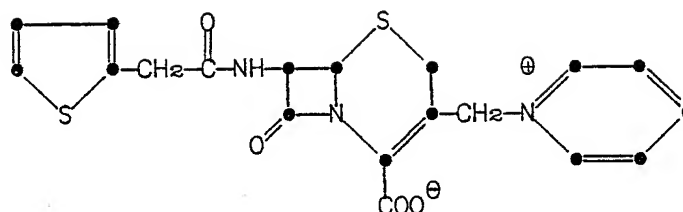
Prior to the present invention, a number of cephalosporin antibiotics substituted in the 3-position by a quaternary ammonium methyl and in the 7-position with various acylamino groups were known. Such compounds possess the zwitterionic structure in that the positively-charged nitrogen atom of the quaternary ammonium group exists in the salt form with the anionic form of the C-4 carboxy group (carboxylate anion) of the cephalosporin. The well-known cephalosporin antibiotic cephaloridine, 7-( $\alpha$ -thienylacetamido)-3-(pyridinium-1-ylmethyl)-3-cephem-4-carboxylate of the following formula, possesses the zwitterionic structure:

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10 The first cephalosporin of this type was discovered by Hale, Newton, and Abraham, Biochem. J. 79, 403 (1961), upon the reaction of cephalosporin C with pyridine (cephalosporin C<sub>A</sub>). Numerous other cephalosporins of this type with differing 7-acylamino side chains have been described since cephalosporin C<sub>A</sub> and cephaloridine were discovered.

15 Recently, Heymes et al., U.S. Patent No. 4,152,432, described cephalosporin antibiotics having as the 7-acylamino side chain a 7-[2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetyl-amino] group and as the 3-position substituent an acetoxymethyl group. Others  
20 have prepared zwitterionic derivatives of this antibiotic, e.g., as described in U.S. Patent No. 4,098,888, by Takeda and in U.S. Patent No. 4,258,041, by O'Callagan et al.

25 Because the cephalosporin antibiotics possess potent antibacterial activity, intensive research to find improved broad spectrum cephalosporin antibiotics continues. In particular, these efforts seek improved cephalosporin antibiotics having potent broad spectrum activity coupled with activity against bacteria and  
30 bacterial strains known to be resistant to antibiotics

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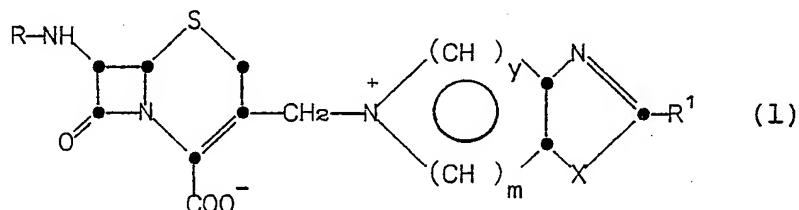
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in current use. This invention provides a new group of cephalosporins having excellent broad spectrum activity.

In accordance with the invention a semi-synthetic cephalosporin of Formula (1)

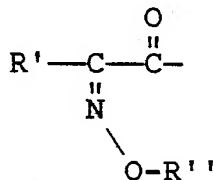
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in which R is hydrogen, formyl,  $\alpha$ -aminoadipoyl, protected  $\alpha$ -aminoadipoyl, or an acyl group represented by the formula

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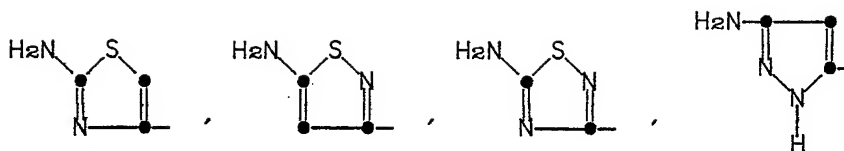


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in which R' is a 5- or 6-membered heterocyclic ring represented by the formulae:

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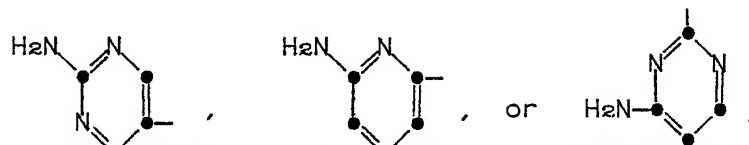
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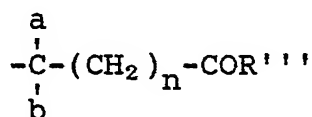
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15  $R''$  is hydrogen,  $C_1-C_4$  alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group represented by the formula



20

25 in which  $n$  is 0-3,  $a$  and  $b$  when taken separately are, independently, hydrogen or  $C_1-C_3$  alkyl, or when taken together with the carbon to which they are attached form a  $C_3-C_7$  carbocyclic ring;  $R'''$  is hydroxy, amino,  $C_1-C_4$  alkoxy, or  $OR^\circ$  in which  $R^\circ$  is indanyl, phthalidyl, an acyloxymethyl group of the formula  $-CH_2-OC(O)R_2$ , in which  $R_2$  is  $C_1-C_4$  alkyl or phenyl; or  $-COOR^\circ$  is a protected carboxy group;

30

or  $R''$  is an N-substituted carbamoyl group represented



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by the formula



5 in which R' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;  
y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

10 R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, is useful as a broad spectrum antibiotic.

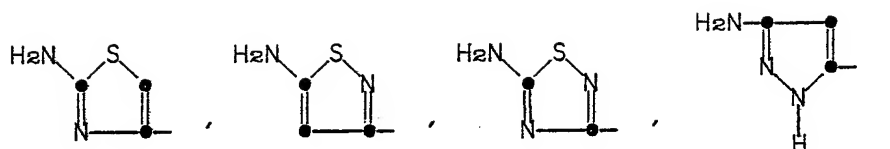
15 A class of such compounds of Formula (1) are those in which R is hydrogen, formyl, α-aminoadipoyl, protected α-aminoadipoyl, or an acyl group of the formula



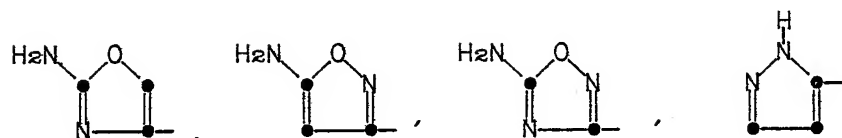
25 in which R' is a 5- or 6-membered heterocyclic ring of the formulae

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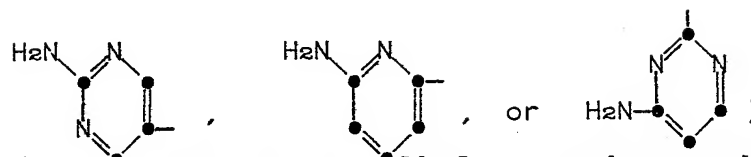
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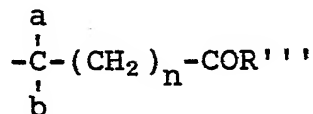
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R'' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:



20

in which n is 0-3; a and b when taken separately are, independently, hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, and when taken together with the carbon to which they are bonded form a C<sub>3</sub>-C<sub>7</sub> carbocyclic ring; R''' is hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, or OR°, in which R° is indanyl, phthalidyl, or an acyloxymethyl group of the formula -CH<sub>2</sub>-O-C(O)-R<sub>2</sub> R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or COOR° is a protected carboxy group;

25

30 or R'' is an N-substituted carbamoyl group of the formula

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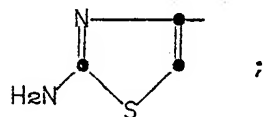


in which R' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

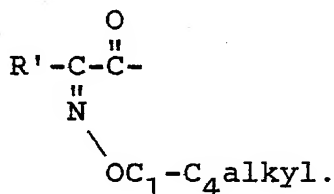
R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, provided that when R' is



R' is C<sub>1</sub>-C<sub>4</sub> alkyl, or n=0, a and b, independently, are hydrogen, methyl, ethyl or when a and b are taken together with the carbon to which they are attached form a C<sub>3</sub>-C<sub>5</sub> carbocyclic ring; y=1 and m=2; and X=S, then R<sup>1</sup> may only be phenyl, thienyl or C<sub>1</sub>-C<sub>4</sub> alkanoylamino.

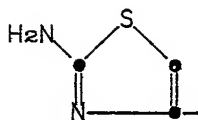
In a preferred embodiment, R is an acyl group of the formula



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Within this group, R' is preferably

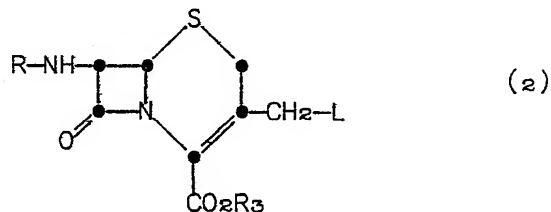


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In another preferred embodiment, X in the above formula is N-R<sup>2</sup> or S. Also preferred are compounds in which y is 1 and m is 2.

Further, in accordance with the invention, there is provided a process for preparing a compound of Formula (1) as defined earlier, or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, which comprises:

(a) condensing a compound of Formula (2):



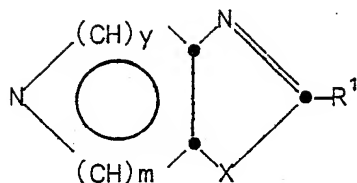
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in which L is a leaving group, R<sub>3</sub> is hydrogen or a carboxy-protecting group, and R is as defined earlier with a bicyclicpyridine compound of the Formula:

25

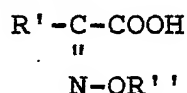
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in which  $y$ ,  $m$ ,  $x$  and  $R^1$  are defined above, removing any protecting group which may be present, and/or salifying or esterifying the product.

(b) acylating a compound of Formula (1) in which  $R$  is hydrogen, or a salt or 4'-ester thereof, with an acid of the Formula:



or an activated derivative thereof, in which  $R'$  and  $R''$  are defined earlier and if desired, removing any protecting group present and/or salifying or esterifying the product.

(c) deacylating a compound of Formula (1) in which  $R$  is other than hydrogen, or a salt or ester thereof to form a compound in which  $R$  is hydrogen, or a salt or ester thereof.

This invention also provides pharmaceutical formulations comprising as an active ingredient a cephalosporin as defined above and a pharmaceutical carrier, excipient or diluent therefor.

Also provided is a method of treating bacterial infections in animals employing a compound provided by this invention.

When used, "C<sub>1</sub>-C<sub>4</sub> alkyl" refers to methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, sec-butyl, and similar groups; "C<sub>1</sub>-C<sub>4</sub> alkoxy" refers to groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, and sec-butoxy; "C<sub>1</sub>-C<sub>3</sub> alkyl" refers to methyl, ethyl, n-propyl, and isopropyl; "C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl" refers to groups such as benzyl, 2-phenethyl, 1-phenethyl, 3-phenylpropyl, and 2-phenylpropyl; and "C<sub>3</sub>-C<sub>7</sub> carbocyclic ring" refers to groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl; and "C<sub>1</sub>-C<sub>4</sub> alkanoylamino" refers to groups such as formamido, acetamido, propionamido, and butyramido.

The term "protected  $\alpha$ -aminoadipoyl" refers to the  $\alpha$ -aminoadipoyl acyl group in which the amino group and the carboxy group are blocked or protected with conventional protecting groups. For example, the amino group can be protected with an acyl or haloacyl group such as acetyl, chloroacetyl, propionyl, benzoyl, chlorobenzoyl, dichloro or dibromobenzoyl, phthaloyl, 2-carboxytetrachlorobenzoyl, or 2-carboxytetrabromobenzoyl; or an alkyloxycarbonyl or aryloxycarbonyl group such as ethoxycarbonyl, trichloroethoxycarbonyl, t-butylloxycarbonyl, t-amylloxycarbonyl, benzyloxycarbonyl, or p-nitrobenzyloxycarbonyl. Conventional carboxy-protecting groups are, for example, the ester forming groups commonly employed in the  $\beta$ -lactam antibiotic art to block or protect the acidic carboxy group during the preparation of the antibiotic compounds. Examples of

such groups are described later for the definition of the term  $R^\circ$  of Formula (1).

The carboxy-substituted alkyl and carboxy-substituted cycloalkyl groups represented by  $R''$  in Formula (1) when  $R'''$  is hydroxy are exemplified by groups such as carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 2-carboxyprop-2-yl, 2-carboxyprop-1-yl, 2-methyl-4-carboxybut-2-yl, 3-carboxy-3-methylprop-2-yl, 1-carboxycycloprop-1-yl, 1-carboxycyclobut-1-yl, 1-carboxycyclopent-1-yl, 1-carboxycyclohex-1-yl, 1-carboxymethylcyclobut-1-yl, or 2-carboxyethylcyclohex-1-yl. When in the above formula  $R'''$  is  $NH_2$ , examples of the carboxamides represented are the amides of the above-named carboxy-substituted radicals.

The esters of the carboxy-substituted groups (Formula (1),  $R''$  is carboxy-substituted alkyl or cycloalkyl and  $R'''$  is  $C_1-C_4$  alkoxy) are illustrated by methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-(ethoxycarbonyl)prop-2-yl, 1-propoxycarbonylcyclopent-1-yl, and similar  $C_1-C_4$  alkyl esters of the above-named carboxy-substituted alkyl and cycloalkyl radicals.

Examples of N-substituted carbamoyl groups (e.g. Formula (1),  $R''$  is carbamoyl) are N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-phenylcarbamoyl, or N-benzylcarbamoyl.

The compounds of this invention are characterized in part by the bicyclic pyridinium group attached to the 3-methyl group of the cephalosporin nucleus. Typical bicyclic pyridines which may be employed in the synthesis of the pyridinium-methyl derivatives of this

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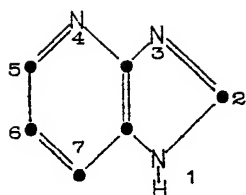
invention are illustrated below. The numbering system employed in the naming of the compounds of the invention is indicated in the following formulae:

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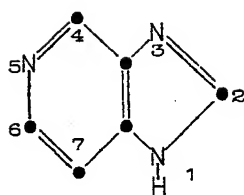


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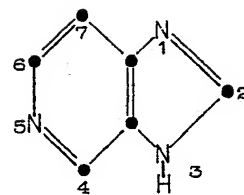
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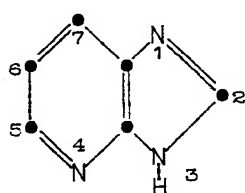
5 1H-imidazo[4,5-b]-pyridine



3H-imidazo[4,5-c]-pyridine

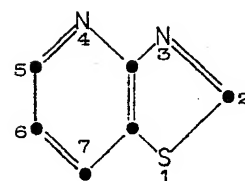


3H-imidazo[4,5-c]-pyridine

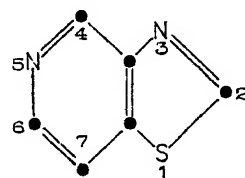


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3H-imidazo[4,5-b]pyridine

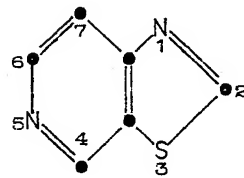


thiazolo[4,5-b]pyridine

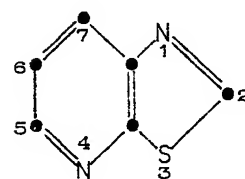


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thiazolo[4,5-c]pyridine

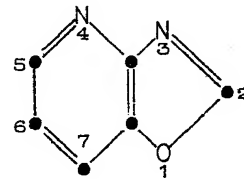


thiazolo[5,4-c]pyridine

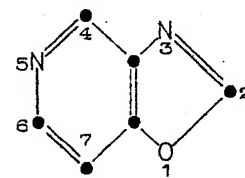


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thiazolo[5,4-b]pyridine

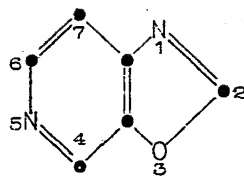


oxazolo[4,5-b]pyridine

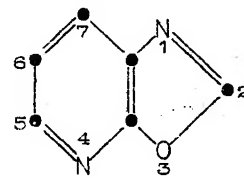


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oxazolo[4,5-c]-pyridine



oxazolo[5,4-c]-pyridine



oxazolo[5,4-b]-pyridine

The imidazolopyridines, oxazolopyridines and thiazolopyridines, the required starting materials, are known compounds which are synthesized employing procedures known in the art.

5 Carboxy-protected derivatives of the compounds represented by the above formula when R'' is a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group and R''' is OR°, are esters of the carboxy group commonly known in the art as carboxy-protecting or  
10 blocking groups. Examples of such ester groups (-COOR°) are those in which R° is alkyl, alkenyl, and substituted alkyl ester groups such as t-butyl, 2-methylbutene-2-yl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, and 2-iodoethyl; the benzyl ester and substituted benzyl esters such as  
15 p-methoxybenzyl and p-nitrobenzyl; the diphenylmethyl ester and substituted diphenylmethyl esters such as the 4-methoxydiphenylmethyl and 4,4'-dimethoxydiphenylmethyl esters; and trialkylsilyl esters such as trimethylsilyl, and other similar ester groups. The carboxy-protecting  
20 group is used for the temporary protection of the carboxy group, for example, during the preparation of the compounds of Formula (1). These groups are removed readily under hydrolytic or hydrogenolytic conditions generally known in the art.

25 The esters defined by Formula (1), when R'' is a carboxy-substituted alkyl or a carboxy-substituted cycloalkyl group and R''' is OR°, namely the indanyl, phthalidyl, and acyloxymethyl esters, are biologically-cleavable esters. Examples of such esters are the  
30 5-indanyl, phthalidyl, acetoxymethyl, propionoxymethyl,

pivaloyloxymethyl, and benzoyloxymethyl esters. The biologically-cleavable esters are obtained by reacting the carboxylic acid function in the salt form, e.g. the sodium or potassium salt, with bromophthalide, or with  
 5 an acyloxymethyl halide, e.g. acetoxymethyl bromide or pivaloyloxymethyl bromide. The indanyl ester is prepared with 5-indanol, the cephalosporin acid and a condensing agent such as DCC or EEDQ.

The heterocyclic rings represented by R' in  
 10 Formula (1) are named as follows: 2-aminothiazol-4-yl, 5-aminoisothiazol-3-yl, 5-amino-1,2,4-thiadiazol-3-yl, pyrazol-5-yl, 3-aminopyrazol-5-yl, 2-aminopyrimidin-5-yl, 4-aminopyrimidin-2-yl, 2-aminopyridin-6-yl, 2-aminooxazol-4-yl, 5-aminoisoxazol-3-yl, and 5-amino-1,2,4-oxadiazol-  
 15 3-yl.

To describe the compounds of the invention, the term "oximino" refers to the oxime and substituted oxime function



The compounds of the invention in which R is an acyl group of the formula

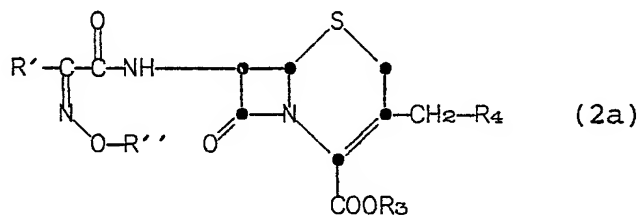


are broad spectrum antibiotics which inhibit the growth  
 30 of microorganisms pathogenic to man and animals. For example, these compounds are effective in controlling

the growth of staphylococci, streptococci and penicillin-resistant strains of staphylococci. They also inhibit the growth of gram-negative bacteria, for example Proteus, Pseudomonas, Enterobacter, Escherichia coli,  
 5 Klebsiella, Shigella, Serratia, and Salmonella.

As described later, the compounds represented by Formula (I) in which R is hydrogen, formyl, amino-adipoyl, or protected amino-adipoyl are intermediates useful in the preparation of the compounds in which R is  
 10 an acyl group.

The compounds in which R is an acyl group are prepared by the reaction of a bicyclicpyridine(imidazolopyridine, oxazolopyridine or thiazolopyridine) with a 7-acylaminocephalosporin represented by Formula (2a)  
 15



20

in which R' and R'' have the same meanings as defined earlier, R<sub>3</sub> is hydrogen or a carboxy-protecting group, and R<sub>4</sub> is a leaving group, preferably chloro, bromo,  
 25 iodo, or acetoxy. The displacement reaction preferably is carried out with a compound of Formula (2a) in which R<sub>4</sub> is acetoxy or iodo. In a preferred method, a compound in which R<sub>4</sub> is iodo is prepared first by reacting, by the method of Bonjouklian, U.S. Patent No. 4,266,049  
 30 issued May 5, 1981, a compound in which R<sub>4</sub> is acetoxy

and  $R_3$  is an ester group, with trimethylsilyliodide (trimethyliodosilane, TMSI). The 3-iodomethyl cephalosporin then is reacted with the bicyclicpyridine to provide a compound of the invention.

5           T perform the process, a compound of Formula (2a) in which  $R_4$  is acetoxy first is silylated to form the silyl ester of the C-4 carboxy group and silyl derivatives of other silyl reactive groups. The silylation is carried out at room temperature in an aprotic  
10 organic solvent with a silylating reagent such as mono- or bis- trimethylsilylacetamide, mono-trimethylsilyltrifluoroacetamide, or N-methyl-N-trimethylsilyltrifluoroacetamide. The silylated derivative then is reacted at ambient temperature with trimethylsilyliodide to provide  
15 the silylated 3-iodomethyl cephalosporin. The silylated 3-iodomethyl cephalosporin then is reacted with the bicyclicpyridine to provide a silylated compound of the invention. Hydrolysis of the silyl groups provides the final desired compound of Formula (I).

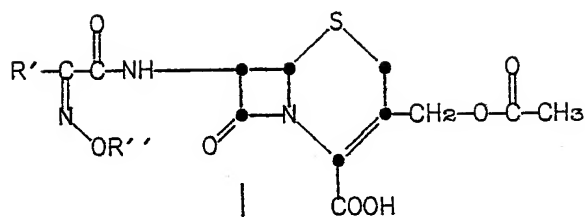
20           The process is illustrated by the following reaction scheme in which a trimethyl silylating reagent and a 1H-imidazolo[4,5-c]pyridine are used.

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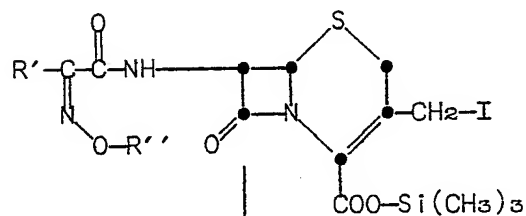
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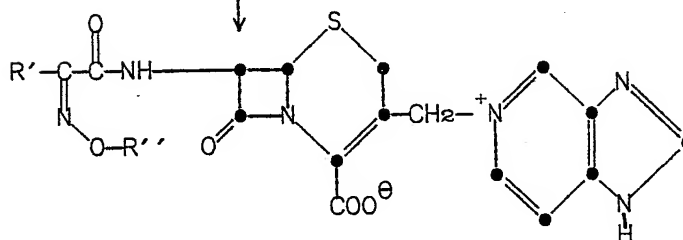
1) silylation  
2) TMSI

10



1) 1H-imidazo[4,5-c]pyridine  
2) hydrolysis

15



20

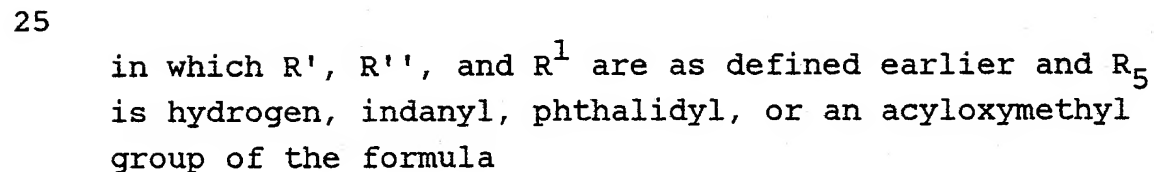
25

In this scheme, R' and R'' have the same meanings as defined earlier.

Alternatively, the antibiotic compounds of the invention are prepared directly from a 3-acetoxymethyl

30

This invention also provides compounds of Formula (1) as salts formed with strong acids and the salt form of biologically-labile esters. Such salts are represented by Formula (3):



in which  $R_2$  is as defined earlier; and  $A^-$  is an anion such as chloride, bromide, iodide, sulfate, or phosphate.

Examples of acyloxymethyl ester groups,  $R_5$ , are acetoxymethyl, propionoxymethyl, pivaloyloxymethyl, and benzoyloxymethyl groups.

A compound of Formula (1) is converted to its strong acid salt by reaction with about one molar equivalent or excess of an acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, or phosphoric acid.

The biologically-labile esters are prepared with a compound of Formula (1) and an acyloxymethyl halide, an indanyl halide, for example, 5-bromoindane or phthalidyl bromide. Upon esterification, the salt form of the ester is obtained. For example, with acetoxymethyl bromide the acetoxymethyl ester bromide is obtained (Formula (3),  $R_5$  is acetoxymethyl,  $A^-$  is  $Br^-$ ).

One skilled in the art will appreciate that if in a compound of Formula (1)  $R''$  is a carboxy-substituted alkyl or cycloalkyl group and  $R'''$  is hydroxy, the di-biologically-labile esters may be prepared. Likewise, acid addition salts will be formed with any basic amino groups present in the molecule (i.e. Formula (1) in which an amino-substituted heterocyclic group is present) when the strong acid salts of Formula (3) are prepared.

The biologically-labile ester salts and the strong acid salts represented by Formula (3) are alternative forms of the compounds of Formula (1) and may be formulated for administration in therapy.



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The compounds of Formula (1), in which R is hydrogen or formyl, are prepared with 7-aminocephalosporanic acid and 7-formamidocephalosporanic acid, respectively, by displacement of the 3-acetoxy group with the bicyclicpyridine as described above. Alternatively, 7-formamido-3-iodomethyl-3-cephem-4-carboxylic acid trimethylsilyl ester is prepared by the Bonjouklian method as described earlier and then is reacted with the bicyclicpyridine to provide the compound of Formula (1) in which R is formyl.

Alternatively, the 7-amino nucleus compounds of Formula (1) (R is H) are prepared by the well-known N-deacylation reaction which proceeds through an imino chloride to an imino ether and upon decomposition of the latter, to the 7-amino-3-bicyclicpyridinium-4-carboxylate. Initially, a 7-acylaminocephalosporanic acid, in which the 7-acyl group can be, for example, phenylacetyl, phenoxyacetyl or a heterocyclic acyl group such as thienylacetyl, is reacted with the bicyclicpyridine to form the 7-acylamino-3-bicyclicpyridinium-methyl)-3-cephem-4-carboxylate. Alternatively, the latter compound is obtained via the 7-acylamino-3-iodomethyl ester (Bonjouklian method) which is allowed to react with the bicyclicpyridine. The 7-acyl bicyclicpyridinium compound then is treated with an imino halide-forming reagent such as phosphorus pentachloride in an inert solvent in the presence of an acid-binding agent such as a tertiary amine, e.g., diethylaniline, to provide the imino halide derivative of the 7-position acylamido group. Without isolation, the imino halide is treated with an alcohol,

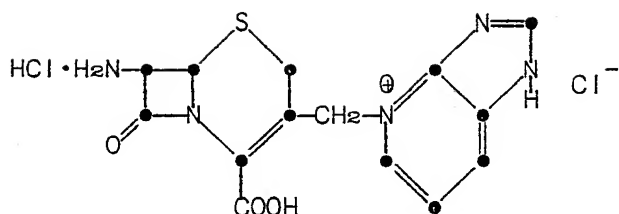
alkanediol or benzyl alcohol to form the corresponding imino ether. Decomposition of the imino ether, for example by aqueous hydrolysis, provides the 7-amino nucleus compound.

- 5           In an example of the preparation of a 7-amino nucleus compound by this method, 7-(2-thienylacetamido)-cephalosporanic acid is reacted with 1H-imidazolo[4,5-b]pyridine to prepare 7-(2-thienylacetamido)-3-(1H-imidazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate. The latter is converted to the trimethylsilyl ester with trimethylchlorosilane in a halogenated hydrocarbon solvent in the presence of a weak base such as dimethylacetamide in an amount corresponding to a 4-5 molar excess. Solvents such as methylene chloride, trichloroethane, and chloroform are suitable. The solution of the silyl ester is cooled to a temperature of about -30°C. to about 0°C. and an imino halide-forming reagent such as phosphorus pentachloride is added. After imino halide formation is complete, a C<sub>1</sub>-C<sub>4</sub> alkanol, an alkanediol, or a benzyl alcohol is added to the cold reaction mixture. The reaction mixture is allowed to warm to about room temperature and the product, 7-amino-3-(1H-imidazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylic acid, precipitates in the form of the dihydrochloride salt represented by the formula:
- 10
- 15
- 20
- 25

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5



The N-formyl compounds (Formula (1), R is  
 10 formyl) are useful as intermediates in the preparation  
 of the antibiotic compounds of the invention. For  
 example, 7-formamidocephalosporanic acid is silylated  
 and the silyl ester converted to the 3-iodomethyl  
 derivative with trimethylsilyliodide as described  
 15 hereinabove. The 3-iodomethyl silylated derivative is  
 reacted with the bicyclicpyridine to form the compound  
 represented by Formula (1). The N-formyl-3-bicyclic-  
 pyridinium-methyl-3-cephem is then converted to the  
 7-amino nucleus compound with methanolic hydrochloric  
 20 acid.

The 7-amino-3-(bicyclicpyridinium methyl)-3-  
 cephem-4-carboxylate or the dihydrochloride salt thereof  
 also is obtained with cephalosporin C in which the amino  
 and carboxy groups are protected. For example, cepha-  
 25 losporin C is first silylated with a conventional  
 silylating reagent such as N-methyl-N-trimethylsilyl-  
 trifluoroacetamide to form the N-trimethylsilyl di-  
 trimethylsilyl ester derivative. The latter is reacted  
 with TMSI by the Bonjouklian method, and the 3-iodo-  
 30 methyl silylated derivative of cephalosporin C obtained

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then is allowed to react with the bicyclicpyridine, and, following hydrolysis of the silyl groups, the compound of the Formula (1) in which R is  $\alpha$ -aminoadipoyl is obtained. The  $\alpha$ -aminoadipoyl side chain is cleaved by  
5 the N-deacylation procedure described above. In carrying out the N-deacylation, the amino group and the carboxy groups of the molecule are protected.

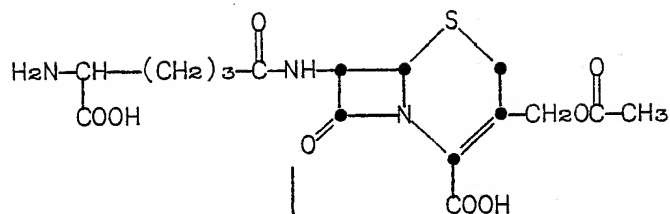
In carrying out the preparation of a 7-amino-3-(bicyclicpyridinium methyl)-3-cephem-4-carboxylate  
10 with Cephalosporin C, the silylated 3-(bicyclicpyridinium methyl) derivative obtained in the Bonjouklian method as described above can be used. Because the amino group and the two carboxy groups are silylated, and thus protected, the N-deacylation can be performed  
15 directly. During the final step of the N-deacylation, i.e. following the formation of the imino ether of the side chain moiety, water is added to effect the hydrolysis of the silyl protecting group. This preparation is illustrated by the following reaction scheme.

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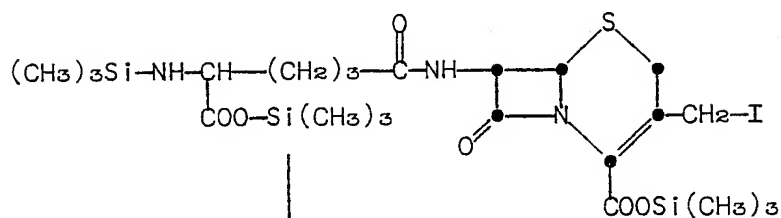
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5



1) Silylation  
2) TMSI

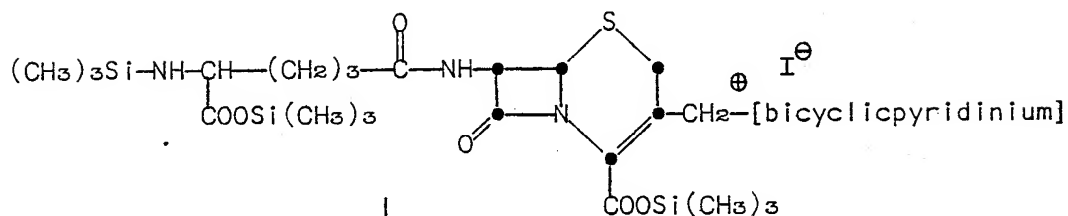
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15

Bicyclicpyridinium

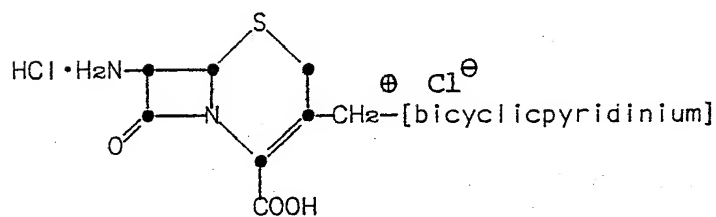
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25

1)  $\text{PCl}_5$   
2) alkanediol  
3)  $\text{H}_2\text{O}$

30

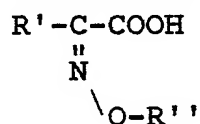


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Alternatively, the 7-amino-3-(bicyclicpyridinium methyl) nucleus compound can be obtained with Cephalosporin C having the amino group and the carboxy groups protected. Examples of protecting groups which  
 5 can be used are given earlier for the definition of the term "protected aminoadipoyl".

The 7-amino nucleus compound (Formula (1), R = H) prepared by the N-deacylation method or via the N-formyl derivative is acylated with a 2-(hetero-  
 10 cyclic)-2-oximinoacetic acid represented by the Formula



15 or an activated derivative thereof, to provide an antibiotic compound of Formula (1). The N-acylation coupling reaction is performed using acylation methods well-known in the art. Active derivatives of the carboxy group such as the so-called "active esters" can  
 20 be used. Examples of active esters are those formed with the oximino acetic acid and hydroxybenzotriazole (HBT), or hydroxysuccinimide; and the esters formed with methyl chloroformate and isobutyl chloroformate. The acylation also can be carried out by employing the acid  
 25 halide, e.g. the acid chloride, in the presence of an acid scavenger such as sodium bicarbonate or triethylamine.

The amino group of the amino-substituted heterocycles (R' in formula 1) desirably is protected  
 30 during the N-acylation of the 7-amino nucleus compound. Amino-protecting groups which can be used are those

commonly employed in the cephalosporin art for the temporary protection of basic amino groups to block or prevent the amino group from interfering with a reaction carried out at another site in the molecule.

5 Examples of such groups are the haloacyl groups such as chloroacetyl and dichloroacetyl; the urethane-forming protecting groups such as t-butyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl,  
10 and diphenylmethyloxycarbonyl; and other protecting groups such as trityl (triphenylmethyl) and benzhydryl.

The compounds represented by Formula (2a) in which  $R_4$  is an acetoxy group are prepared by known methods. For example, compounds in which  $R'$  is the 2-  
15 aminothiazol-4-yl group are described by Heymes et. al., U.S. Patent No. 4,152,432; compounds in which  $R'$  is 2-aminopyridin-6-yl, 2-aminopyrimidin-5-yl, or 4-aminopyrimidin-2-yl, are described in U.S. Patent No. 4,167,176; compounds in which  $R'$  is 5-amino-1,2,4-  
20 thiadiazol-3-yl are described in EPO Publication No. 0,007,470; compounds in which  $R'$  is 2-aminooxazol-4-yl, 5-amino-1,2,4-oxadiazol-3-yl or 5-aminoisoxazol-3-yl are described in U.S. Patent No. 4,406,898; compounds in which  $R''$  is an N-substituted carbamoyl group are  
25 prepared by methods described in U.S. Patent No. 4,200,575; and compounds in which  $R'$  is 3-aminopyrazol-5-yl, or pyrazol-5-yl are obtained as described in U.K. Patent Application 2,046,734A.

Commonly, the compounds of Formula (2a) in  
30 which  $R_4$  is acetoxy are prepared by the N-acylation of

the 7-amino group of 7-aminocephalosporanic acid, or an ester thereof, with the 2-(heterocyclic)-2-oximinoacetic acid by employing acylation methods known in the art. For example, the heterocyclic oximino-substituted acetic acid is converted to an active ester, such as the ester  
5      formed with hydroxybenzotriazole or hydroxysuccinimide, and the active ester is used as the acylating moiety. Other active derivatives of the carboxylic acid such as the acid chloride or acid azide can be used in the  
10     acylation.

          The compounds of Formula (2) in which R' is a pyrazol-5-yl or 3-aminopyrazol-5-yl group are prepared by employing methods known in the art. The 2-(pyrazol-5-yl)-2-oximinoacetic acid or the 2-(3-aminopyrazol-5-yl)-2-oximinoacetic acid is prepared and converted to an  
15     active derivative of the carboxylic acid, for example, an active ester. The active ester is used to N-acylate 7-aminocephalosporanic acid. The resulting 7-[2-(pyrazol-5-yl)-2-oximinoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid and 7-[2-(3-aminopyrazol-5-yl)-2-oximinoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid are converted to the corresponding 3-iodomethyl  
20     silylated derivatives as described earlier. The latter may be reacted with, for example, thienopyridine to  
25     provide the respective compound of the invention.

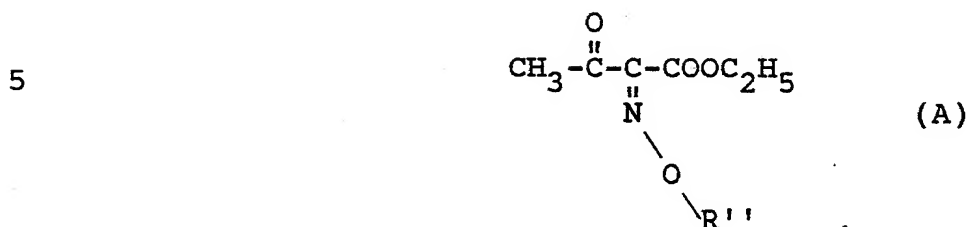
          The pyrazole and aminopyrazole oximino substituted acetic acids are prepared by synthetic methods known in the art. For example, the 2-(pyrazol-5-yl)-2-alkoxyiminoacetic acid is prepared by heating in an



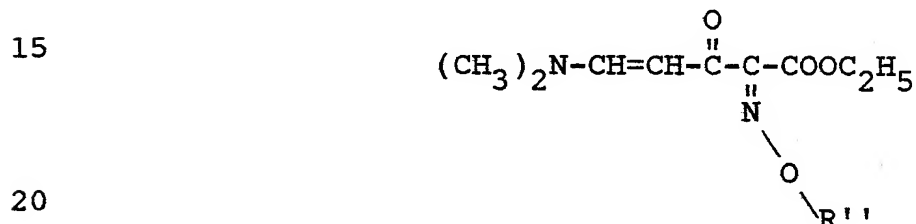
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inert hydrocarbon solvent the acetyl oximino compound of formula (A):



in which R'' is as defined above but is other than hydrogen, with dimethylformamide dimethylacetal to form the dimethylaminomethylene oximino ester of the formula

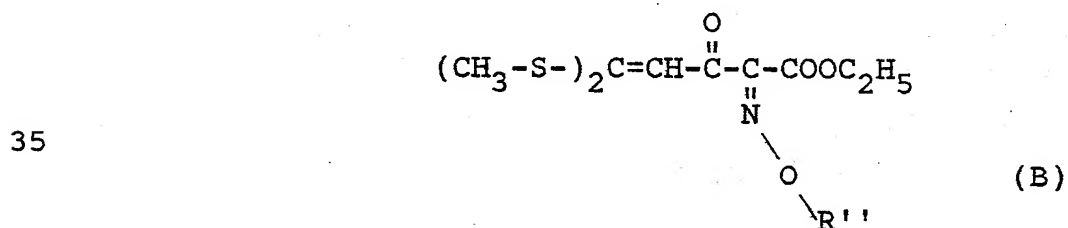


The latter is reacted with hydrazine hydrate to provide the ethyl ester of 2-(pyrazol-5-yl)-2-alkoxyiminoacetic acid. The ester is hydrolyzed to the free acid and the acid converted to an active ester for acylation.

25

The 2-(3-aminopyrazol-5-yl)-2-alkoxyiminoacetic acid is prepared by reacting the compound of formula (A) with carbon disulfide and two equivalents of methyl iodide to form the intermediate compound of formula (B)

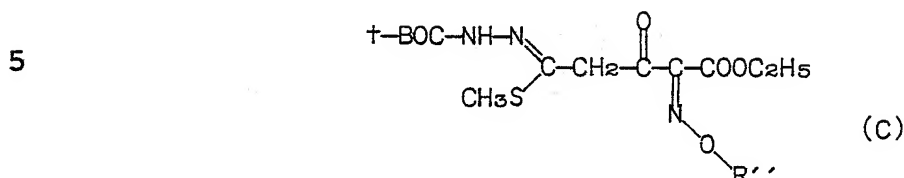
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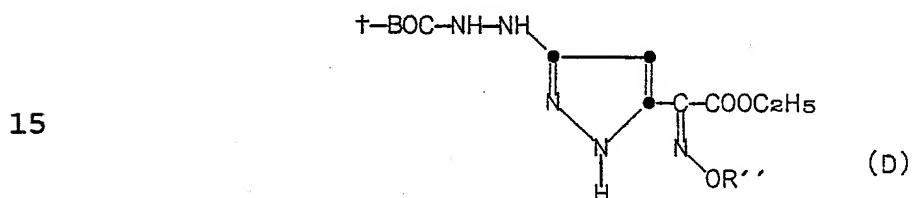
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Intermediate (B) is reacted with N-t-BOC hydrazine to provide compound (C),



and (C) is reacted with hydrazine hydrate to form  
10 2-(3-t-BOC-hydrazinopyrazol-5-yl)-2-oximinoacetic acid ethyl ester (D).



Compound (D) is treated with trifluoroacetic acid to remove the t-BOC group and the 3-hydrazinopyrazole is  
20 nitrosated with nitrous ( $\text{HNO}_2$ ) acid, in the cold, to form 2-(3-azidopyrazol-5-yl)-2-oximinoacetic acid ethyl ester. The azido group is reduced to the amino group by chemical reduction to provide the 2-(3-aminopyrazol-5-yl)-oximinoacetic acid ethyl ester. The ester is  
25 hydrolyzed under alkaline conditions to the free acid.

The compounds of the invention have the same stereochemistry as known cephalosporin antibiotics. The 7-position side chain has the natural  $\beta$ -configuration (6R, 7R), while the oximino group in the side chain can  
30 exist in the syn or anti forms or as a mixture of both.

Compounds of the invention in either form are prepared by employing the 2-(heterocyclic)-2-oximinoacetic acid acylating moiety in the syn or anti form. Alternatively, mixtures of the syn and anti compounds of Formula (1) can be separated by chromatographic means such as by HPLC. The compounds in the syn form are preferred because of their higher activity.

Examples of bicyclicpyridinium compounds of Formula (1) in which R is an acyl group may include the following compounds:

7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1H-imidazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-ethoxycarbonylmethoxyiminoacetamido]-3-(3H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3H-imidazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(thiazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(thiazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-  
acetamido]-3-(thiazolo[5,4-c]pyridinium-5-ylmethyl)-3-  
cephem-4-carboxylate,

5 7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-  
acetamido]-3-(thiazolo[5,4-b]pyridinium-4-ylmethyl)-3-  
cephem-4-carboxylate,

7-[2-(2-aminopyridin-6-yl)-2-(2-carboxyprop-  
yl)xyiminoacetamido]-3-(oxazolo[4,5-b]pyridinium-4-  
ylmethyl)-3-cephem-4-carboxylate,

10 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxy-  
iminoacetamido]-3-(oxazolo[4,5-c]pyridinium-5-ylmethyl)-  
3-cephem-4-carboxylate,

15 7-[2-(5-aminoisothiazol-3-yl)-2-(2-carboxyprop-  
2-yl)oxyiminoacetamido]-3-(oxazolo[5,4-c]pyridinium-5-  
ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminopyrimidin-5-yl)-2-ethoxyimino-  
acetamido]-3-(oxazolo[5,4-b]pyridinium-4-ylmethyl)-3-  
cephem-4-carboxylate,

20 7-[2-(4-aminopyrimidin-2-yl)-2-(N-methylcar-  
bamoyloxy)iminoacetamido]-3-(1H-2-methylimidazolo[4,5-  
b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminopyridin-6-yl)-2-methoxyimino-  
acetamido]-3-(3H-2-phenylimidazolo[4,5-b]pyridinium-  
4-ylmethyl)-3-cephem-4-carboxylate,

25 7-[2-(3-aminopyrazol-5-yl)-2-methoxyimino-  
acetamido]-3-(2-ethylthiazolo[5,4-c]pyridinium-5-  
ylmethyl)-3-cephem-4-carboxylate,

30 7-[2-(2-aminooxazol-4-yl)-2-ethoxycarbonyl-  
methoxyiminoacetamido]-3-(2-aminooxazolo[5,4-c]pyri-  
dinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(pyrazol-5-yl)-2-methoxycarbonylmethoxy-  
iminoacetamido]-3-(2-acetamidothiazolo[5,4-c]pyridinium-  
5-ylmethyl)-3-cephem-4-carboxylate,

5 7-[2-(pyrazol-5-yl)-2-ethoxycarbonylmethoxy-  
iminoacetamido]-3-(2-(2-thienyl)oxazolo[5,4-c]pyridinium-  
5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(5-aminoisoxazol-3-yl)-2-methoxyimino-  
cetamido]-3-(2-aminooxazolo[5,4-b]pyridinium-4-ylmethyl)-  
3-cephem-4-carboxylate,

10 7-[2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-  
2-yl)oxyiminoacetamido]-3-(1H-2-aminoimidazolo[4,5-  
c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

15 7-[2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-  
yl)oxyiminoacetamido]-3-(1,2-dimethylimidazolo[4,5-  
c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(5-amino-1,2,4-oxadiazol-3-yl)-2-(2-car-  
boxyprop-2-yl)oxyiminoacetamido]-3-(1-methyl-2-phenyl-  
3H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-  
carboxylate,

20 7-[2-(2-aminothiazol-4-yl)-2-(2-carboxy-  
prop-2-yl)oxyiminoacetamido]-3-(2-formamidothiazolo[4,5-  
b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,

25 7-[2-(2-aminopyridin-6-yl)-2-methoxyimino-  
acetamido]-3-(2-aminothiazolo[4,5-c]pyridinium-5-  
ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminopyridin-6-yl)-2-methoxyimino-  
acetamido]-3-(2-n-butylthiazolo[5,4-c]pyridinium-5-  
ylmethyl)-3-cephem-4-carboxylate,

- 7-[2-(2-aminopyridin-6-yl)-2-ethoxycarbonyl-methoxyiminoacetamido]-3-(2-aminothiazolo[5,4-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 5 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-oximinoacetamido]-3-(2-phenyloxazol[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-phenyloxazol[5,4-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,
- 10 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-isopropylthiazolo[5,4-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-ethyl-1-propyl-1H-imidazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 15 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-(1,2-dimethyl-3H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,
- 7-[2-(pyrazol-5-yl)-2-ethoxycarbonylmethoxyiminoacetamido]-3-(2-(2-thienyl)thiazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 20 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-phenyloxazol[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 25 7-[2-(5-aminoisoxazol-3-yl)-2-methoxyiminoacetamido]-3-(2-isopropylloxazol[5,4-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,
- 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-phenyloxazol[5,4-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate,
- 30

7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-  
acetamido]-3-(2-aminooxazolo[4,5-c]pyridinium-5-yl-  
methyl)-3-cephem-4-carboxylate,

5 7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-  
acetamido]-3-(2-aminothiazolo[4,5-c]pyridinium-5-yl-  
methyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-  
2-yl)oxyiminoacetamido]-3-(2-isobutylthiazolo[5,4-  
c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

10 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-  
methoxyiminoacetamido]-3-(2-butyramido-1H-imidazolo[4,5-  
c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(pyrazol-5-yl)-2-ethoxycarbonylmethoxy-  
iminoacetamido]-3-[1,2-diethyl-3H-imidazolo[4,5-c]pyri-  
15 dinium-5-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-  
acetamido]-3-(2-acetamidothiazolo[5,4-b]pyridinium-4-  
ylmethyl)-3-cephem-4-carboxylate,

20 7-[2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-  
2-yl)oxyiminoacetamido]-3-(2-isobutyloxazolo[4,5-b]pyri-  
dinium-4-ylmethyl)-3-cephem-4-carboxylate,

7-[2-(2-aminopyrimidin-5-yl)-2-ethoxyimino-  
acetamido]-3-(2-methyloxazolo[5,4-b]pyridinium-4-yl-  
methyl)-3-cephem-4-carboxylate,

25 7-[2-(2-aminothiazol-4-yl)-2-hydroxyimino-  
acetamido]-3-(thiazolo[5,4-c]pyridinium-5-ylmethyl)-  
3-cephem-4-carboxylate,

7-[2-(3-aminopyrazol-5-yl)-2-methoxyimino-  
acetamido]-3-(2-phenylthiazolo[5,4-b]pyridinium-4-yl-  
30 methyl)-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-(2-(2-thienyl)-3H-imidazolo-[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate, and

5 7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(2-aminooxazolo[5,4-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate.

A preferred group of compounds are those represented by Formula (1) in which X is  $N-R^2$  or S.  
10 Preferred compounds of the invention also are represented by Formula (1) in which R is an acyl group and R' is 2-aminothiazol-4-yl and R'' is  $C_1-C_4$  alkyl, preferably methyl, or a carboxy-substituted alkyl group, preferably 2-carboxyprop-2-yl, 2-carboxymethyl, or  
15 2-carboxyethyl.

The following non-limiting examples are provided to further illustrate the invention.

In the Examples, TMSI is trimethylsilyliodide; THF is tetrahydrofuran; HPLC is high performance liquid  
20 chromatography; NMR is nuclear magnetic resonance spectrum; DMSO- $d_6$  is deuterated dimethylsulfoxide; and the letters characterizing the NMR signals are as follows: s is singlet, d is doublet, q is quartet, m is multiplet, t is triplet, v is very, and b is broad. The  
25 NMR spectra were run on a JEOL FX-90.

#### Preparation 1

3H-Imidazolo[4,5-c]pyridine was prepared by  
30 the method of Stanovik and Tisler, Synthesis, 2, 120



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(1974). A mixture of 2.2 g (0.02 mole) of 3,4-diaminopyridine and 5 ml of diethoxymethyl acetate was heated at reflux for two hours. The reaction mixture was cooled and diluted by addition of ethyl acetate. The solid precipitate was collected by filtration and sublimed at 170°C (50 torr) to give 0.84 g of 3H-imidazolo[4,5-c]pyridine; mp 165-168°C.

Analysis calc. for  $C_6H_5N_3$

Theory: C, 60.50; H, 4.23; N, 35.27.

Found: C, 60.15; H, 4.32; N, 34.94.

#### Preparations 2-4

Following the general procedure of Preparation 1, the following imidazolopyridines were prepared:

1H-imidazolo[4,5-c]pyridine; mp 164-166°C.

3-methyl-3H-imidazolo[4,5-c]pyridine; mp 82-88°C.

1-methyl-1H-imidazolo[4,5-c]pyridine; mp 80°C.

#### Preparation 5

A mixture 15.0 g of 3,4-diaminopyridine and 100 ml of acetic anhydride was heated at 120°C for seventy hours. The reaction mixture was cooled, concentrated and made alkaline to pH 11 by addition of 5N sodium hydroxide. The alkaline solution was extracted with chloroform and the extracts were combined, dried, and concentrated to dryness to give 5.8 g of 1H-2-methyl-imidazolo[4,5-c]pyridine; mp 164-166°C.

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Preparations 6-7

Similarly prepared were:

5 1,2-Dimethyl-1H-imidazolo[4,5-c]pyridine; mp  
171-173°C.

2,3-Dimethyl-3H-imidazolo[4,5-c]pyridine; M<sup>+</sup>  
Theory 147; Found 147.

Preparation 8-9

10

A mixture of 1.1 g (10 mM) of 3,4-diaminopyri-  
dine, 1.3 g (10 mM) of thiophene-2-carboxylic acid, and  
50 g of polyphosphoric acid was heated at 160°C for four  
hours. The reaction mixture was added to 100 g of ice  
15 and stirred for fifteen minutes. The precipitated solid  
was collected by filtration and dried to give 500 mg of  
2-(2-thienyl)-1H-imidazolo[4,5-c]pyridine; mp 265-268°C.

Similarly prepared was 2-phenyl-1H-imidazolo-  
[4,5-c]pyridine; 730 mg, single spot tlc (silica,  
20 chloroform-methanol; 90:10 v/v).

Preparation 10

A mixture of 20 g (0.18 mole) of 2-amino-3-  
25 hydroxypyridine in 80 ml of water containing 20 g (0.19  
mole) of cyanogen bromide was heated at reflux for fif-  
teen minutes. The reaction mixture was filtered and the  
filtrate was cooled, neutralized by addition of sodium  
bicarbonate, and the precipitate that formed was col-  
30 lected by filtration and dried to give, following

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recrystallization from ethanol and water, 8.66 g of 2-aminooxazolo[4,5-b]pyridine; mp 220-222°C.

Preparation 11

5

3-Amino-4-hydroxypyridine was reacted with acetic anhydride to afford 4.7 g of 2-methyloxazolo[4,5-c]pyridine; mp 56-58°C.

10

Preparation 12

Following the procedure of Takahashi, Chem. Pharm. Bull. (Tokyo) 2, (1954), 963 mg of 3-nitropyridine-4-thiol was reacted with 28.89 g of formic acid and 6.42 g of iron filings to provide, following purification over a silica gel column, 860 mg of thiazolo[4,5-c]pyridine; mp 101-104°C.

15

Preparation 13

20

A mixture of 1.3 g of 3-nitropyridine-4-thiol in 4 ml of acetic acid and 15 ml of acetic anhydride containing 1.5 g of zinc dust was heated at reflux for four hours. The reaction mixture was cooled and concentrated to an oil. The oil was dissolved in 5N sodium hydroxide and the alkaline solution was extracted with diethyl ether. The extracts were combined, dried and concentrated to dryness to afford 557 mg of 2-methylthiazolo[4,5-c]pyridine.  $M^+$  Theory 150; Found 150.

25

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Preparation 14

3-Nitropyridine-4-thiol was reacted with propionic acid, propionic anhydride and zinc to give 2-ethylthiazolo[4,5-c]pyridine; mp 35°C.

Preparation 15

According to the method described in J. Het. Chem., 14(1), 129(1977) 2-chloro-3-aminopyridine was reacted with potassium thiocyanate and hydrochloric acid in ethanol to produce 45.3 g of 2-aminothiazolo[5,4-b]pyridine.  $M^+$  Theory 151; Found 151.

Example 1

syn-7-[2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-(1H-imidazolo[4,5-c]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

To a suspension of 1.34 g (2.5 mM) of syn-7-[2-(2-aminothiazol-4-yl)-2-(tert-butoxycarbonylprop-2-yl)oxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 15 ml of dichloromethane were added in one portion 1.42 ml (8 mM) of N-methyl-N-trimethylsilyltrifluoroacetamide. The reaction mixture was stirred for five minutes at 25°C under nitrogen. To the stirred solution was added by pipette 0.88 ml (6.2 mM) of TMSI and the reaction mixture then was stirred at 25°C for thirty minutes. The solvent was removed by evaporation under reduced pressure to provide an oil. The oil was

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dissolved in 6 ml of acetonitrile and 0.84 ml (10.3 mM) of tetrahydrofuran and the solution was stirred for five minutes, whereupon a solution of 325 mg (2.7 mM) of 1H-imidazolo[4,5-c]pyridine (from Preparation 2) in 2 ml of acetonitrile containing 1 ml of N-methyl-N-trimethylsilyltrifluoroacetamide was added in one portion. The reaction mixture was stirred for three hours at 25°C and then added to a mixture of 60 ml of diethyl ether, 35 ml of acetone and 5 ml of methanol. The precipitated solid was collected by filtration to provide 630 mg (23% yield) of the product as a solid. The solid was purified by reverse phase C<sub>18</sub> silica HPLC using acetonitrile-acetic acid-water (10-2-88% by volume) as eluant. Removal of the solvents from the appropriate fractions afforded 120 mg of syn-7-[2-(2-aminothiazol-4-yl)-2-carboxyprop-2-yl)oxyiminoacetamido]-3-(1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate.

IR(KBr): 1776 cm<sup>-1</sup> β-lactam;  
UV (EtOH) λ<sub>max</sub> 220 ε 37,000;  
M<sup>+</sup> Theory 586; Found 586;  
NMR (DMSO-d<sub>6</sub>): signals at 9.75 (s, 1H) δ 9.5 (d, 1H); 8.1 (d, 1H); 8.7 (d, 1H); 7.1 (bs, 2H); 6.7 (s, 1H); 5.7 (m, 1H); 5.15 (d, 1H); 1.4 (s, 6H);

25

Example 2

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

A suspension of 910 mg (2 mM) of syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 5 ml of dichloromethane containing 1.24 ml (7 mM) of N-methyl-N-trimethylsilyltrifluoroacetamide was warmed to 40°C and sonicated for five minutes. The reaction mixture was cooled to 25°C and stirred while 0.77 ml (5.4 mM) of TMSI were added, and then stirring was continued at 25°C for thirty minutes. The solvent was removed by evaporation under reduced pressure and the oil was dissolved in 3 ml of acetonitrile and 0.77 ml (9 mM) of tetrahydrofuran. To this reaction mixture was added a solution of 297 mg (2.5 mM) of 1H-imidazolo[4,5-c]pyridine in 12 ml of acetonitrile containing 1.5 ml of N-methyl-N-trimethylsilyltrifluoroacetamide. The reaction mixture was stirred at 25°C for three hours and then added to 50 ml of 95% acetone-methanol (v/v). The precipitated solid was collected by filtration (yield 1.09 g) and purified by reverse phase C<sub>18</sub> silica HPLC using acetonitrile-acetic acid-water (4-2-94 percent by volume). There were obtained 390 mg of syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate.

IR(KBr): 1772 cm<sup>-1</sup> β-lactam;  
UV (EtOH) λ<sub>max</sub> 212 ε 34,000;  
M<sup>+</sup> Theory 515; Found 515;  
NMR (DMSO-d<sub>6</sub>): signals at δ 9.85 (s, 1H); 9.55 (d, 1H); 8.9 (d, 1H); 8.8 (s, 1H); 8.15 (d, 1H); 7.2 (bs, 2H); 6.7 (s, 1H); 5.7 (m, 1H); 5.15 (d, 1H); 3.8 (s, 3H).

Example 3

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyimino-acetamido]-3-(3-methyl-3H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate was prepared according to the procedure of Example 2 by reacting 910 mg (2 mM) of syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl 4-carboxylic acid with 1.24 ml (7.0 mM) of N-methyl-N-trimethylsilyltrifluoroacetamide and 0.77 ml (5.4 mM) of TMSI to produce the corresponding 3-iodomethyl cephalosporin, and reacting the latter compound in situ with 3-methyl-3H-imidazolo[4,5-c]pyridine. The product was obtained as 920 mg of a white solid. Purification over C<sub>18</sub> reverse phase HPLC gave 340 mg of title compound.

IR(KBr): 1772 cm<sup>-1</sup>;  
UV (EtOH)  $\lambda_{\text{max}}$  210  $\epsilon$  36,500;  
M<sup>+</sup> Theory 529; Found 529;  
NMR (DMSO-d<sub>6</sub>): signals at  $\delta$  9.5 (d, 1H) 9.4 (d, 1H); 9.05 (s, 1H); 8.35 (d, 1H), 7.2 (bs, 2H); 6.73 (s, 1H); 5.75 (m, 1H), 5.15 (d, 1H); 4.15 (s, 3H), 3.83 (s, 3H).

Examples 4-16

The following 3-bicyclicpyridiniummethyl cephalosporins were prepared by the methods of Examples 1-3 by reacting a bicyclic pyridine with a 3-iodomethyl cephalosporin derived from the corresponding 3-acetoxymethyl cephalosporin derivative:

Example 4

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 86%  
IR(KBr): 1773  $\text{cm}^{-1}$   $\beta$ -lactam;  
 $\text{M}^+$  Theory 529; Found 529.  
NMR ( $\text{DMSO-d}_6$ ): signals at  $\delta$  10.1 (s, 1H), 9.45 (d, 1H);  
9.1 (d, 1H), 8.8 (s, 1H), 8.3 (d, 1H), 7.15 (bs, 2H),  
10 6.65 (s, 1H), 5.65 (m, 1H), 5.05 (m, 1H), 4.0 (s, 3H),  
3.75 (s, 3H).

Example 5

15 syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 96%.  
NMR ( $\text{DMSO-d}_6$ ): signals at  $\delta$  9.9 (s, 1H), 9.5 (d, 1H),  
8.85 (d, 1H); 8.05 (d, 1H), 7.1 (bs, 2H), 6.66 (s, 1H),  
20 5.7 (m, 1H), 5.1 (d, 1H), 3.75 (s, 3H) 2.7 (s, 3H).

Example 6

25 syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1,2-dimethyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 80%  
IR(KBr): 1774  $\text{cm}^{-1}$   $\beta$ -lactam;  
UV (EtOH)  $\lambda_{\text{max}}$  218  $\epsilon$  48,500.



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NMR (DMSO- $d_6$ ): signals at  $\delta$  9.8 (s, 1H), 9.5 (d, 1H), 9.1 (d, 1H), 8.2 (d, 1H), 7.15 (bs, 2H), 6.65 (s, 1H), 5.6 (m, 1H), 5.05 (m, 1H); 3.9 (s, 3H), 3.75 (s, 3H), 2.7 (s, 3H).

5

Example 7

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxy-iminoacetamido]-3-(2,3-dimethyl-3H-imidazolo[4,5-c]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 53%

IR(KBr): 1775  $\text{cm}^{-1}$   $\beta$ -lactam;

UV (EtOH)  $\lambda_{\text{max}}$  206  $\epsilon$  38,000;

$M^+$  Theory 543; Found 543.

15 NMR (DMSO- $d_6$ ): signals at  $\delta$  9.9 (s, 1H), 9.5 (d, 1H), 9.3 (d, 1H), 8.1 (d, 1H), 7.15 (bs, 2H), 6.7 (s, 1H), 5.7 (m, 1H), 5.1 (d, 1H), 3.95 (s, 3H), 3.8 (s, 3H), 2.8 (s, 3H).

20

Example 8

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxy-iminoacetamido]-3-[2-(2-thienyl)-1H-imidazolo[4,5-c]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 18.7%

25

IR(KBr): 1774  $\text{cm}^{-1}$   $\beta$ -lactam;

UV (EtOH)  $\lambda_{\text{max}}$  247  $\epsilon$  25,500;

$M^+$  Theory 596; Found 597.

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NMR (DMSO- $d_6$ ): signals at  $\delta$  9.5 (d, 1H), 9.3 (s, 1H), 8.5 (d, 3H), 7.8 (m, 2H), 7.2 (bs, 2H), 6.7 (s, 1H), 5.7 (m, 1H), 5.1 (d, 1H), 3.8 (s, 3H).

5

Example 9

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-phenyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 620 mg.

10 IR(KBr): 1772  $\text{cm}^{-1}$   $\beta$ -lactam;

UV (EtOH)  $\lambda_{\text{max}}$  242  $\epsilon$  39,500;

$M^+$  Theory 591; Found 591.

NMR (DMSO- $d_6$ ): signals at  $\delta$  9.5-7.5 (m, 8H), 7.1 (s, 2H), 6.7 (s, 1H), 5.7 (m, 1H), 5.15 (d, 1H), 3.8 (s,

15 3H).

Example 10

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-aminooxazolo[4,5-b]pyridinium-4-ylmethyl)-3-cephem-4-carboxylate. Yield 100%

IR(KBr): 1772  $\text{cm}^{-1}$   $\beta$ -lactam;

1695

1656

25 UV (EtOH)  $\lambda_{\text{max}}$  205, 235, 315  $\epsilon$  22,746.

NMR (DMSO- $d_6$ ): signals at  $\delta$  9.5 (d, 1H), 9.05 (d, 1H), 8.1 (d, 1H), 7.33 (d, 1H), 7.1 (bs, 2H), 6.7 (s, 1H), 5.6 (m, 1H), 5.0 (d, 1H), 3.8 (s, 3H).

Example 11

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyloxazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 74%  
IR(KBr): 1776  $\text{cm}^{-1}$   $\beta$ -lactam;  
UV (EtOH)  $\lambda_{\text{max}}$  203  $\epsilon$  41,500;  
 $\text{M}^+$  Theory 530; Found 530.  
NMR ( $\text{DMSO-d}_6$ ): signals at  $\delta$  10.2 (s, 1H), 9.5 (m, 2H),  
8.5 (d, 1H), 5.6 (m, 1H), 5.0 (d, 1H), 3.8 (s, 3H), 2.8 (s, 3H).

Example 12

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(thiazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 95%  
IR(KBr): 1773  $\text{cm}^{-1}$   $\beta$ -lactam;  
NMR ( $\text{DMSO-d}_6$ ): signals at  $\delta$  10.4 and 9.9 (d, 4H), 7.7 (s, 1H), 6.1 (d, 1H), 3.8 (s, 3H).

Example 13

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methylthiazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate. Yield 48%  
IR(KBr): 1777  $\text{cm}^{-1}$   $\beta$ -lactam;  
1674  
1623  
UV (EtOH)  $\lambda_{\text{max}}$  227, 260  $\epsilon$  21,975;

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NMR (DMSO- $d_6$ ): signals at  $\delta$  10.15 (s, 1H), 9.5 (d, 1H), 9.25 (d, 1H), 8.75 (d, 1H), 5.6 (m, 1H), 5.0 (d, 1H), 3.8 (s, 3H), 2.95 (s, 3H).

5

Example 14

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamido]-3-(2-ethylthiazolo[4,5-c]pyridinium-5-yl-methyl)-3-cephem-4-carboxylate.

10 IR(KBr): 1772  $\text{cm}^{-1}$   $\beta$ -lactam;

UV (EtOH)  $\lambda_{\text{max}}$  230  $\epsilon$  46,500;

$M^+$  Theory 559; Found 560.

NMR (DMSO- $d_6$ ): signals at  $\delta$  10.15 (s, 1H), 9.35 (d, 1H), 8.8 (d, 1H), 5.6 (m, 1H), 5.0 (d, 1H), 3.8 (s, 3H), 3.3

15 (q, 2H), 1.4 (t, 3H).

Example 15

syn-7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamido]-3-(2-aminothiazolo[5,4-b]pyridinium-4-yl-methyl)-3-cephem-4-carboxylate. Yield 100%

UV (EtOH)  $\lambda_{\text{max}}$  250  $\epsilon$  25,633;

Analysis calculated for  $\text{C}_{20}\text{H}_{18}\text{N}_8\text{O}_5\text{S}_3$

Theory: C, 43.95; H, 3.32; N, 20.50; S, 17.60.

25 Found: C, 42.07; H, 3.80; N, 17.84; S, 15.71.

NMR (DMSO- $d_6$ ): signals at  $\delta$  9.5 (d, 1H), 8.75 (m, 3H), 8.1 (d, 1H), 7.73 (m, 1H), 5.6 (m, 1H), 5.0 (d, 1H), 3.8 (s, 3H).

Titration (66% dimethylformamide in water v/v)  $\text{pK}_a$  at

30 4.0, 7.4, 10.7.

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Example 16

5        syn-7-[2-(2-aminothiazolo-4-yl)-2-methoxyimino-  
acetamido]-3-(2-methylthiazolo[5,4-c]pyridinium-5-yl-  
methyl)-3-cephem-4-carboxylate.

UV (EtOH)  $\lambda_{\max}$  253  $\epsilon$  20,563;

IR (KBr) 1774  $\text{cm}^{-1}$  ( $\beta$ -lactam);

$M^+$  Theory 546; Found 546.

10                The 3-bicyclicpyridinium methyl cephalosporins  
provided by this invention are useful as antibiotic sub-  
stances. The compounds have demonstrated excellent  
antibacterial activity against a wide variety of Gram +  
and Gram - bacilli. The compounds are particularly ef-  
15        fective against diseases caused by Steptococci, H. in-  
fluenza, E. coli, Klebsiella, Enterobacter, Salmonella,  
and Serratia.

20                The antibacterial activity of several repre-  
sentative compounds of the invention has been evaluated  
in standard in vitro agar dilution assays. The follow-  
ing Table presents typical minimum inhibitory concentra-  
tions (MIC's) in  $\mu\text{g/ml}$  for exemplary compounds when  
evaluated against several Gram + and Gram - microorgan-  
isms. The activity of the known compound, ceftazidime,  
25        is given for comparison.

---

Table I

Agar Dilution MIC ( $\mu\text{g/ml}$ )

Organism	Strain	Ceftazidime	Compound of Example No.						
			1	2	3	4	5	6	7
Staph. aureus	X1.1	8	8	1	1	1	2	2	2
	V41	32	32	8	4	8	8	16	16
	X400	128	128	64	64	64	32	32	128
	S13E	32	32	8	4	8	8	8	16
Staph. epi	EPI1	16	32	4	2	2	4	2	4
	222	16	16	1	1	1	1	1	2
	C203	0.125	0.06	<0.008	<0.008	0.15	<0.008	<0.008	0.015
	PARK	0.125	0.06	<0.008	<0.008	0.15	<0.008	<0.008	-
Strep. A	X66	>128	>128	>128	>128	>128	>128	>128	>128
	9960	16	16	2	4	2	8	4	4
	C.L.	0.125	0.03	0.015	0.06	0.06	0.015	0.06	0.06
	76	0.125	0.06	0.015	0.06	0.06	0.015	-	0.03
E. coli	N10	0.25	0.5	0.015	0.06	0.03	0.03	0.03	0.03
	EC14	0.125	0.125	<0.008	<0.008	<0.008	<0.008	<0.008	0.015
	TEM	0.125	0.125	<0.008	<0.008	0.015	<0.008	<0.008	0.015
	X26	0.06	0.125	<0.008	<0.008	0.015	<0.008	<0.008	0.015
Klebsiella	KAE	0.5	1.0	4	4	4	2	2	2
	X68	0.125	0.125	<0.008	0.03	0.015	0.015	0.03	0.03
Enterobacter aerogenes cloacae	C32	0.25	1.0	0.03	0.06	0.03	0.03	0.03	0.03
	EB5	0.125	0.25	0.06	0.06	0.03	0.06	0.03	0.03
	X514	0.125	0.5	<0.008	<0.008	0.05	<0.008	0.03	0.03
	X528	2	8	1.0	1	1	2	4	4
Pseudomonas	X239	2	2	2	2	2	2	4	4
	X99	0.25	0.5	0.015	0.06	0.06	0.03	0.03	0.03

Table I (cont'd)

		Compound of Example No.											
		8	9	10	11	12	13	14	15				
Organism	Strain	Agar Dilution MIC ( $\mu\text{g/ml}$ )											
Staph. aureus	X1.1	2	2		0.5	1	1	1					
	V41	8	8	4	8	2	8	4	2				
	X400	32	32	32	32	2	32	32	32				
	S13E	8	8	4	8	8	8	4	4				
Staph. epi	EPI1	4	4	2	4	2	2	2	2				
	222	2	2	1	1	-	1	1	16				
	C203	<0.008	<0.008	0.015	0.015	0.015	0.015	<0.008	0.015				
Strep. A	PARK	<0.008	<0.008	0.015	0.015	0.015	<0.008	<0.008	-				
Strep. PN	X66	>128	>128	>128	>128	128	>128	>128	128				
Strep. D	9960	4	4	16	8	4	8	4	8				
H. influ.	C.L.	0.25	0.5	0.06	0.125	0.06	0.03	0.06	0.06				
	76	-	-	0.125	0.06	0.06	0.03	0.015	0.06				
E. coli	N10	1	1	0.125	0.06	0.03	0.03	0.03	0.03				
	EC14	0.25	0.125	0.06	0.03	0.015	0.015	0.015	0.06				
	TEM	0.03	0.06	0.03	0.03	0.03	0.015	0.015	0.03				
	X26	0.015	0.015	0.03	0.015	0.015	0.015	<0.008	0.03				
Klebsiella	KAE	4	2	4	4	4	2	2	-				
	X68	0.5	0.5	0.06	0.06	0.03	0.03	0.03	4				
Enterobacter	aerogenes	0.5	0.5	0.125	0.06	0.03	0.03	0.06	0.03				
	cloacae	0.5	0.5	0.25	0.125	0.06	0.06	0.06	0.06				
	Salmonella	0.5	0.5	0.06	0.03	0.03	0.06	0.06	0.03				
	Pseudomonas	64	64	4	4	1	2	4	1				
	X239	64	64	2	2	2	8	4	2				
	Serratia	0.5	1.0	0.125	0.125	0.06	0.06	0.06	0.06				

The excellent antibacterial activity of the compounds provided by this invention make them particularly attractive agents for the treatment of a number of diseases of bacterial origin. The treatment of animals suffering from bacterial diseases, or suspected of developing a bacterial infection, is thus another embodiment of this invention. The antibacterial method of treatment provided by this invention is practiced by administering an antibacterially-effective amount of a 3-bicyclicpyridinium methyl cephalosporin antibiotic as defined herein to an animal in need of treatment. The method can be practiced therapeutically or prophylactically. The amount of active antibiotic to be administered according to the method will vary depending upon the particular compound selected, the severity of the disease being treated or guarded against, the individual undergoing treatment, and related factors commonly encountered with such treatments. Normally, however, the compounds will be administered at a dose of about 0.5 to about 50 mg/kg of animal body weight, and more preferably at a rate of about 1 to about 10 mg/kg. Such amounts may be administered once each day, or more often as needed to treat the particular disease or subject undergoing treatment according to the present method. A typical daily dose for an average adult human will be about 200 to about 500 mg per day.

The antibiotic compounds provided by this invention are especially active when administered by the parenteral route, but they can be formulated for any desired route of administration. Such formulations



constitute yet another embodiment of this invention. The formulations of this invention will comprise from about 0.1 to about 95 percent by weight of an active cephalosporin antibiotic of the invention (compounds of  
5 Formula (1) in which R is acyl), admixed with a pharmaceutically-acceptable carrier, diluent or excipient therefor. Typical formulations may contain from about 10 to about 60 percent by weight of active ingredient, and more preferably about 20 to about 50 percent.

10 For convenient oral administration, the compounds can be admixed with any of a number of diluents, excipients and carriers commonly employed in oral formulations, and molded into tablets, pills, troches, or encapsulated into gelatin capsules. Typical car-  
15 riers, diluents and excipients commonly employed include potato starch, corn starch, sucrose, dextrose, microcrystalline cellulose, dicalcium phosphate, alginic acid, acacia; lubricants such as magnesium stearate; binders such as gum tragacanth or gelatin; and flavoring  
20 agents such as peppermint oil, cherry or strawberry flavoring, or oil of wintergreen. The compounds also can be formulated as syrups or elixirs employing common diluents such as a fatty oil, methyl or propyl parabens, suitable dyes and flavoring agents. The compounds also  
25 can be formulated in the form of a buccal seal, lozenge or other suitable device for sustained controlled delivery of the active ingredient over a prolonged period.

30 The antibiotics of the invention preferably are formulated for parenteral administration, for

example via the intravenous, intramuscular or subcutaneous routes, as well as the transdermal route. Such compositions normally will contain from about 0.1 to about 20.0 percent by weight of active ingredient.

5 Typical excipients, diluents and carriers for parenteral formulations include isotonic saline, dilute aqueous dextrose (e.g. 5%), the polyhydric aliphatic alcohols or mixtures thereof, for instance, glycerin, propylene glycol, or polyethylene glycol. Parenteral solutions  
10 also may contain preservatives such as phenethylalcohol, methyl and propyl parabens, and thimerosal. If needed, about 0.05 to about 0.20 percent by weight of an antioxidant such as sodium metabisulfite or sodium bisulfite also can be employed. For intravenous use, preferred  
15 formulations will employ an initial concentration down to about 0.05 to about 0.25 mg/ml of active ingredient, and for intramuscular injection, a preferred concentration of active ingredient is about 0.25 to about 0.50 mg/ml.

20 Examples of typical pharmaceutical formulations may include the following.

Example 17

25 Formulation for Intravenous Use		
Ingredient		Amount
Compound of Example 2		1.0 g
0.9% saline		100 ml

X-6050

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The intravenous solution can be prepared, for example, with a unit dosage formulation of the antibiotic in a plastic bag or similar container, and by adding the diluent to the container prior to infusion.

5

Example 18

## Formulation of Oral Suspension

	Ingredient	Amount
10	Compound of Example 8	500 mg
	Sorbitol solution (70% N.F.)	40 ml
	Sodium benzoate	150 mg
	Saccharin	10 mg
	Cherry flavor	50 mg
15	Distilled water q s ad	100 ml

The sorbitol solution is added to 40 ml of distilled water and the cephalosporin is suspended thereon. The saccharin, sodium benzoate, and flavoring are added and dissolved. The volume is adjusted to 100 ml with distilled water. Each ml of syrup contains 5 mg of the cephalosporin antibiotic. This oral formulation is suited ideally for pediatric use.

25

Example 19

## Preparation of 250 mg capsule

Ingredient	Amount
Compound of Example 10	250 mg

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Lactose	150 mg
Corn starch	<u>100 mg</u>
	500 mg

5           The ingredients are blended to uniformity and encapsulated into gelatin capsules. Such capsules may be administered orally at the rate of about one each day for the treatment of upper respiratory bacterial infections, including pharyngitis and tonsillitis.

10

Example 20

Preparation of Parenteral Solution

15           In a solution of 700 ml of propylene glycol and 200 ml of distilled water for injection is dissolved 20.0 grams of the compound of Example 1, as the hydrochloride salt. The pH of the solution is adjusted to 5.5 with hydrochloric acid, and the volume is made up to 1000 ml with distilled water. The formulation is

20           sterilized, filled into 5.0 ml ampoules each containing 2.0 ml (representing 40 mg of active ingredient) and sealed under nitrogen.

25           The compounds of the invention additionally may be administered intrarectally, for example in a suitably formulated suppository. Pharmaceutically-acceptable suppository formulations can be prepared with the antibiotic compound and a suppository composition such as cocoa butter, hydrogenated fats, glycerides, or polyethylene glycols.

X-6050

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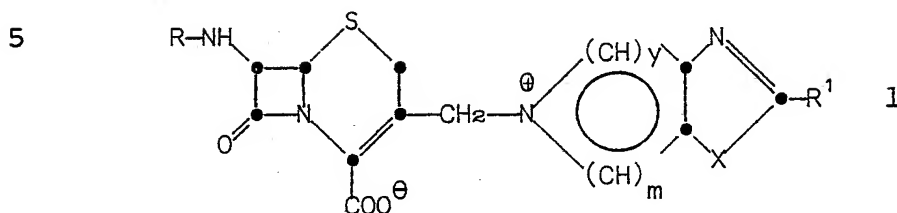
Pharmaceutical compositions of the invention also include unit dosage formulations. Such formulations comprise between about 200 mg. and about 10 g. of the antibiotic or a pharmaceutically-acceptable salt thereof in solid form in a sterile ampoule, vial or a plastic container such as a bag adapted for i.v. administration. The antibiotic may be amorphous or in the crystalline state. Such formulations may also contain a buffering agent, solubilizing agent, clarifying agent, stabilizing agent, or other excipient. An example of a pharmaceutical composition of this invention for i.v. use comprises 500 mg. of the dry powder of the antibiotic or a pharmaceutically acceptable salt thereof in a 10 ml. sterile rubber-stoppered ampoule. Another such composition comprises 4 g. of dry powder of the antibiotic in a 100 ml. sterile ampoule. A further composition comprises 10 g. of the antibiotic as a dry powder in a sealed, sterile plastic pouch.

X-6050-(EPO')

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CLAIMS

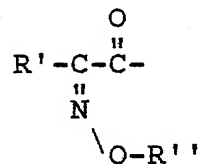
1. A compound of Formula (1):



10

in which R is hydrogen, formyl,  $\alpha$ -aminoadipoyl, protected  $\alpha$ -aminoadipoyl, or an acyl group of the formula

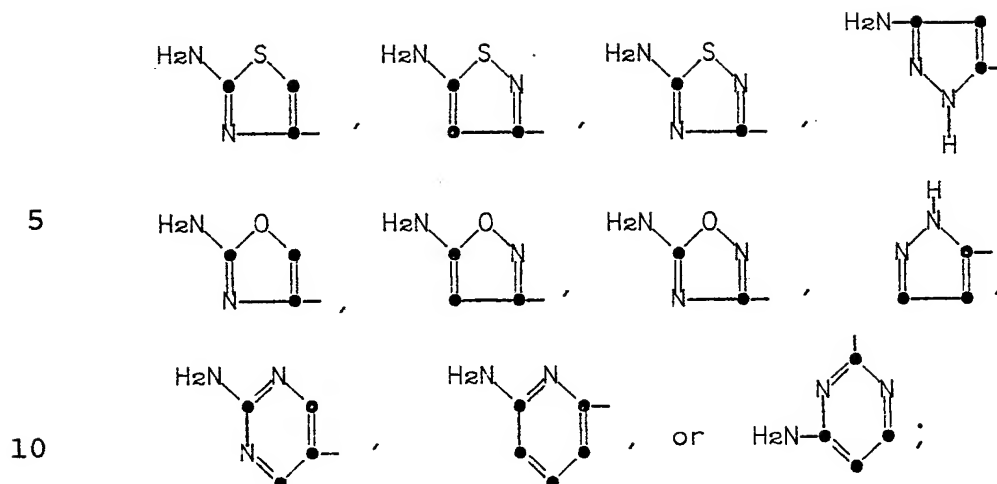
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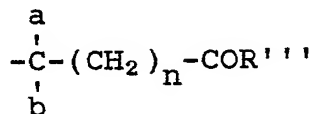
in which R' is a 5- or 6-membered heterocyclic ring of the formulae

X-6050-(EPO')

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15  $R''$  is hydrogen,  $C_1$ - $C_4$  alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:



20 in which  $n$  is 0-3;  $a$  and  $b$  when taken separately are, independently, hydrogen or  $C_1$ - $C_3$  alkyl, and when taken together with the carbon to which they are bonded form a  $C_3$ - $C_7$  carbocyclic ring;

25  $R'''$  is hydroxy,  $C_1$ - $C_4$  alkoxy, amino, or  $OR^\circ$ , in which  $R^\circ$  is indanyl, phthalidyl, or an acyloxymethyl group of the formula  $-CH_2-O-C(O)-R_2$  in which  $R_2$  is  $C_1$ - $C_4$  alkyl or phenyl; or  $COOR^\circ$  is a protected

30 carboxy group;

or  $R''$  is an N-substituted carbamoyl group of the formula

X-6050-(EPO')

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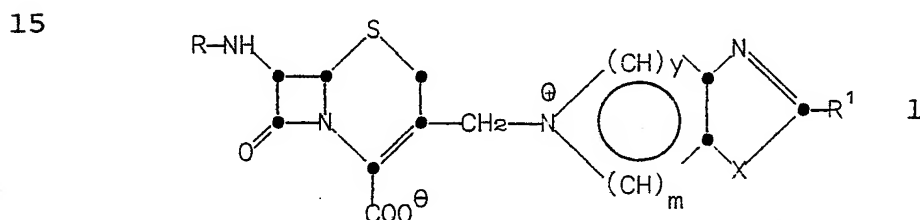
in which R'''' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof.

2. A compound of Formula (1):



in which R is hydrogen, formyl, α-aminoadipoyl, protected α-aminoadipoyl, or an acyl group of the formula



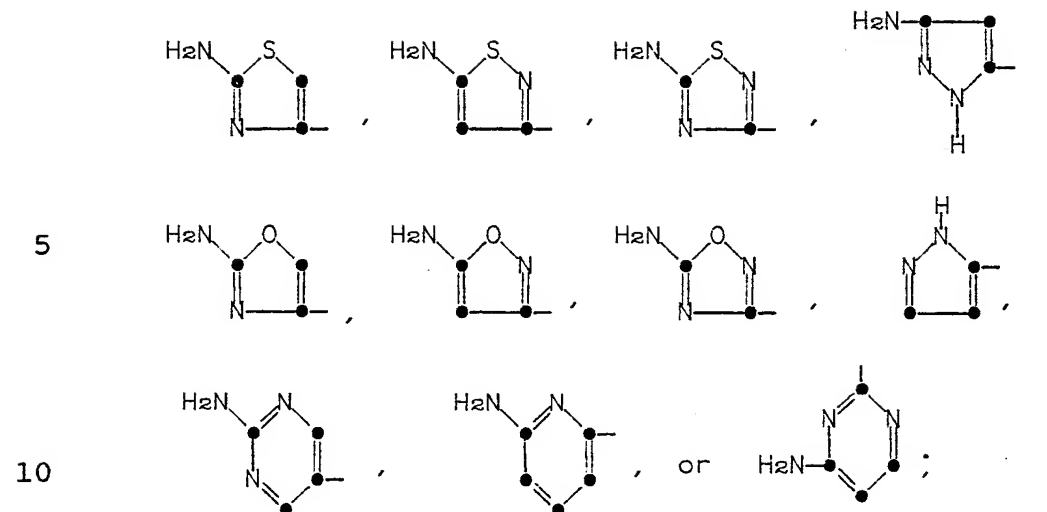
in which R' is a 5- or 6-membered heterocyclic ring of the formulae

30

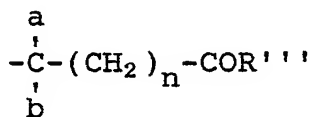


X-6050-(EPO')

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15 R' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:



20 in which n is 0-3; a and b when taken separately are, independently, hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, and when taken together with the carbon to which they are bonded form a C<sub>3</sub>-C<sub>7</sub> carbocyclic ring; R''' is hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, or OR°, in which R° is indanyl, phthalidyl, or an acyloxymethyl group of the formula -CH<sub>2</sub>-O-C(O)-R<sub>2</sub> in which R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or COOR° is a protected

25

30 carboxy group;

or R' is an N-substituted carbamoyl group of the formula

X-6050-(EPO')

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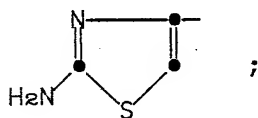
in which R' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, provided that when R' is

15



and R' is C<sub>1</sub>-C<sub>4</sub> alkyl, or if n=0, and a and b, independently, are hydrogen, methyl, ethyl or when a and b are taken together with the carbon to which they are attached form a C<sub>3</sub>-C<sub>5</sub> carbocyclic ring; and y=1 and m=2; and X=S, then R<sup>1</sup> may only be phenyl, thienyl or C<sub>1</sub>-C<sub>4</sub> alkanoylamino.

3. A compound of Formula (1), or a pharmaceutically-acceptable salt or ester thereof, as claimed in claim 1 or 2 in which R' is 2-amino-thiazol-4-yl.

4. A compound of Formula (1), or a pharmaceutically-acceptable salt or ester thereof, as claimed in claim 3 in which y is 1 and m is 2.

5. A compound of Formula (1), as claimed in any one of claims 1 to 4 in which X is N-R<sup>2</sup> or O.

6. A compound of Formula (1), as claimed in any one of claims 1 to 4 in which X is S.

5        7. syn-7-[2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-(1H-imidazolo[4,5-c]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

10        syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-methyl-3H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

15        syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

20        syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1,2-dimethyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazole-4-yl)-2-methoxyiminoacetamido]-3-(2,3-dimethyl-3H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

25        syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(2-thienyl)-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazole-4-yl)-2-methoxyiminoacetamido]-3-(2-phenyl-1H-imidazolo[4,5-b]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

5 syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-aminooxazolo[4,5-b]-pyridinium-4-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyloxazolo[4,5-c]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

10 syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-aminothiazolo[5,4-b]-pyridinium-4-ylmethyl)-3-cephem-4-carboxylate  
or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof.

15 8. syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(thiazolo[4,5-c]-pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methylthiazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

20 syn-7-[2-(2-aminothiazolo-4-yl)-2-methoxyiminoacetamido]-3-(2-methylthiazolo[5,4-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate.

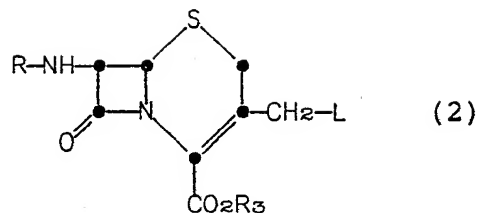
syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-ethylthiazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof.

9. A process for preparing a cephalosporin derivative of Formula (1) or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, as claimed in any one of claims 1 to 8, which comprises:

(a) condensing a compound of Formula (2):

X-6050-(EPO')

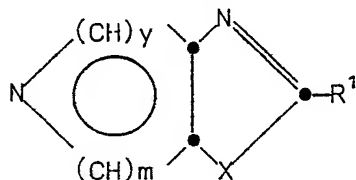
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5

in which L is a leaving group,  $R_3$  is hydrogen or a carboxy-protecting group, and R is as defined in claim 1 or 2; with a bicyclicpyridine compound of the Formula:

10

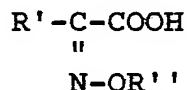


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and if desired, removing any protecting group which may be present, and/or salifying or esterifying the product.

20

(b) acylating a compound of Formula (1) in which R is hydrogen, or a salt or 4'-ester thereof, with an acid of the Formula:



25

or an activated derivative thereof, and if desired, removing any protecting group present and/or salifying or esterifying the product.

30

(c) deacylating a compound of Formula (1) in which R is other than hydrogen, or a salt or

X-6050-(EPO')

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ester thereof to form a compound in which R is hydrogen, or a salt or ester thereof.

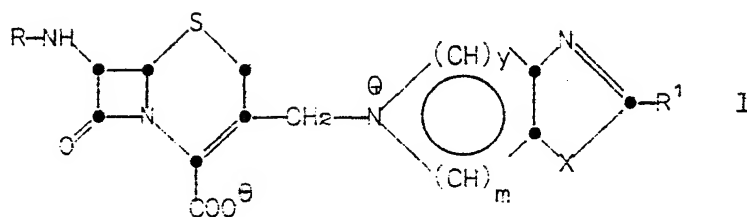
10. A compound of Formula (1), or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, as claimed in any one of claims 1 to 8  
5 for use as an antibiotic.

11. A pharmaceutical formulation which comprises as an active ingredient, a compound of Formula (1), in which R is an acyl group, or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof,  
10 as claimed in any one of claims 1 to 8, associated with one or more pharmaceutically-acceptable carriers, excipients or diluents therefor.

CLAIMS

1. A process for preparing a compound of  
Formula (1):

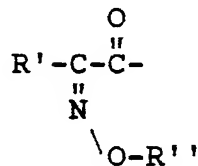
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in which R is hydrogen, formyl,  $\alpha$ -aminoadipoyl, pro-  
tected  $\alpha$ -aminoadipoyl, or an acyl group of the formula

15

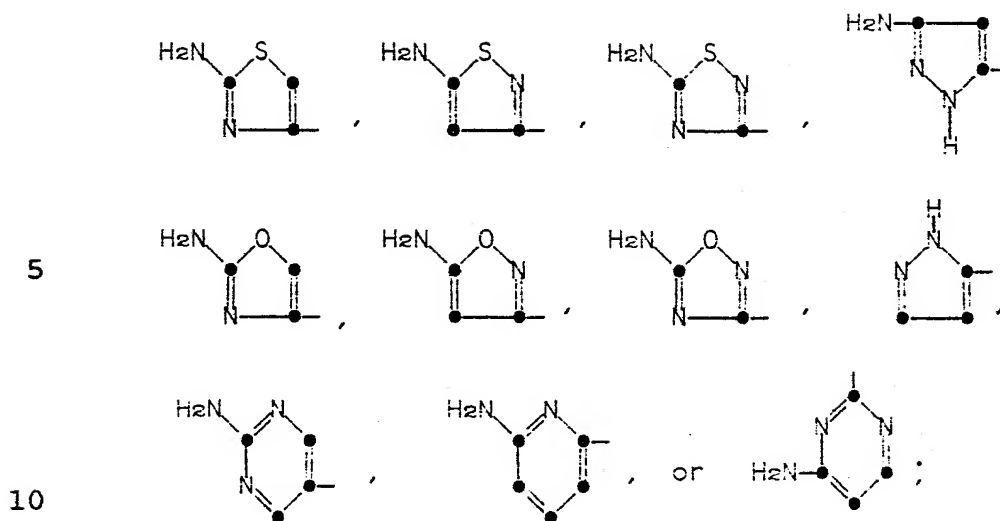


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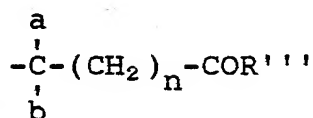
in which R' is a 5- or 6-membered heterocyclic ring of  
the formulae

X-6050-(P')

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15 R'' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:



20 in which n is 0-3; a and b when taken separately are, independently, hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, and when taken together with the carbon to which they are bonded form a C<sub>3</sub>-C<sub>7</sub> carbocyclic ring;

25 R''' is hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, or OR°, in which R° is indanyl, phthalidyl, or an acyloxymethyl group of the formula -CH<sub>2</sub>-O-C(O)-R<sub>2</sub> in which R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or COOR° is a protected

30 carboxy group;

or R'' is an N-substituted carbamoyl group of the formula



X-6050-(P')

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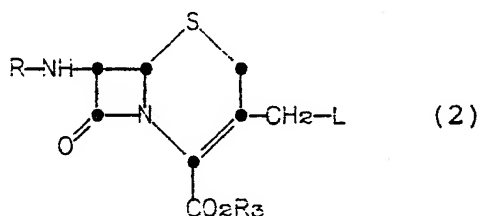
in which R'''' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

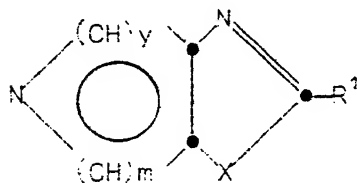
R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, which comprises

(a) condensing a compound of Formula (2):



in which L is a leaving group, R<sub>3</sub> is hydrogen or a carboxy-protecting group, and R is as defined in claim 1 or 2; with a bicyclicpyridine compound of the Formula:

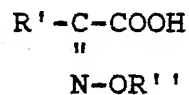


and if desired, removing any protecting group which may be present, and/or salifying or esterifying the product.

X-6050-(P')

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(b) acylating a compound of Formula (1) in which R is hydrogen, or a salt or 4'-ester thereof, with an acid of the Formula:



5

or an activated derivative thereof, and if desired, removing any protecting group present and/or salifying or esterifying the product.

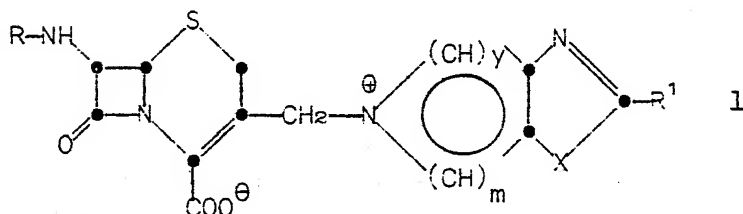
10

(c) deacylating a compound of Formula (1) in which R is other than hydrogen, or a salt or ester thereof to form a compound in which R is hydrogen, or a salt or ester thereof.

15

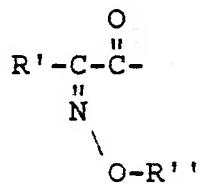
2. A process for preparing a compound of Formula (1):

20



25

in which R is hydrogen, formyl,  $\alpha$ -aminoadipoyl, protected  $\alpha$ -aminoadipoyl, or an acyl group of the formula

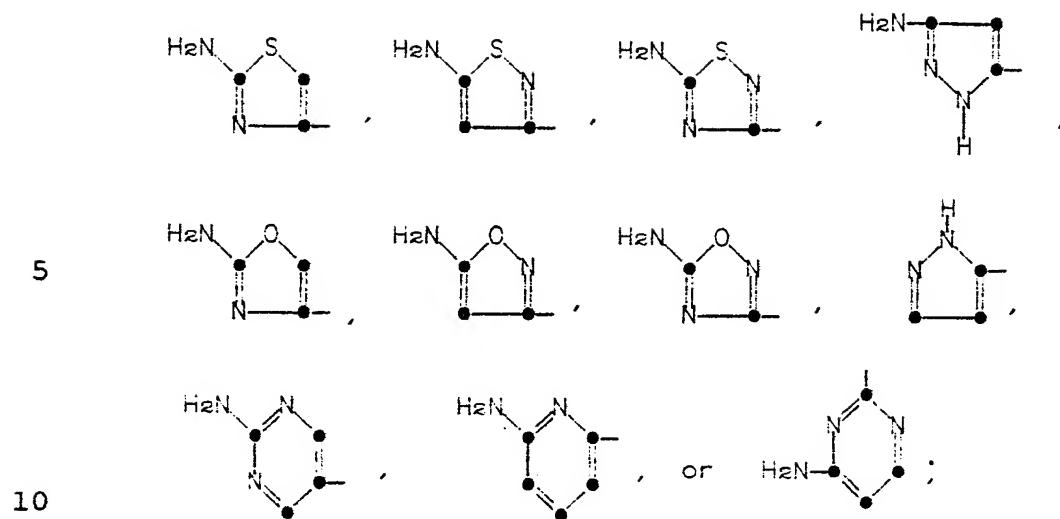


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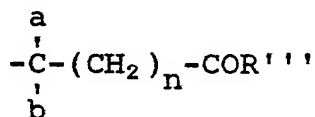
in which R' is a 5- or 6-membered heterocyclic ring of the formulae

X-6050-(P')

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15 R' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:



20 in which n is 0-3; a and b when taken separately are, independently, hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, and when taken together with the carbon to which they are bonded form a C<sub>3</sub>-C<sub>7</sub> carbocyclic ring;

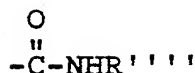
25 R'' is hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, or OR°, in which R° is indanyl, phthalidyl, or an acyloxymethyl group of the formula -CH<sub>2</sub>-O-C(O)-R<sub>2</sub> in which R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or COOR° is a protected

30 carboxy group;

or R' is an N-substituted carbamoyl group of the formula

X-6050-(P')

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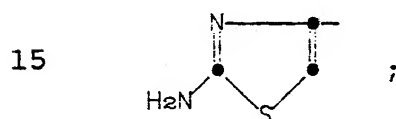


in which R'''' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

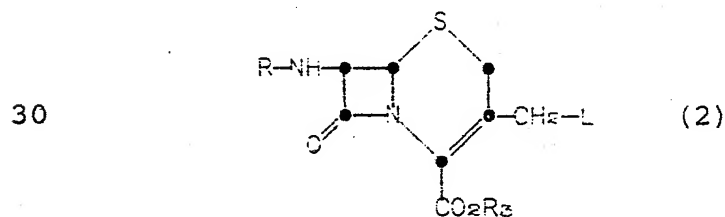
R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof, provided that when R' is



and R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, or if n=0, and a and b, independently, are hydrogen, methyl, ethyl or when a and b are taken together with the carbon to which they are attached form a C<sub>3</sub>-C<sub>5</sub> carbocyclic ring; and y=1 and m=2; and X=S, then R<sup>1</sup> may only be phenyl, thienyl or C<sub>1</sub>-C<sub>4</sub> alkanoylamino, said process comprising

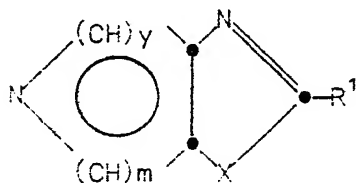
(a) condensing a compound of Formula (2):



X-6050-(P')

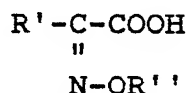
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in which L is a leaving group,  $R_3$  is hydrogen or a carboxy-protecting group, and R is as defined in claim 1 or 2; with a bicyclicpyridine compound of the Formula:



and if desired, removing any protecting group which may be present, and/or salifying or esterifying the product.

(b) acylating a compound of Formula (1) in which R is hydrogen, or a salt or 4'-ester thereof, with an acid of the Formula:



or an activated derivative thereof, and if desired, removing any protecting group present and/or salifying or esterifying the product.

(c) deacylating a compound of Formula (1) in which R is other than hydrogen, or a salt or ester thereof to form a compound in which R is hydrogen, or a salt or ester thereof.

3. A process for preparing a compound of Formula (1), or a pharmaceutically-acceptable salt or ester thereof, as claimed in claim 1 or 2 in which R' is 2-amino-thiazol-4-yl.

4. A process for preparing a compound of Formula (1), or a pharmaceutically-acceptable salt or ester thereof, as claimed in claim 3 in which y is 1 and m is 2.

5 5. A process for preparing a compound of Formula (1), as claimed in any one of claims 1 to 4 in which X is N-R<sup>2</sup> or O.

6. A process for preparing a compound of Formula (1), as claimed in any one of claims 1 to 4 in  
10 which X is S.

7. A process as claimed in any one of claims 1 to 6 for preparing

syn-7-[2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-(1H-imidazolo[4,5-c]-  
15 pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-  
3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-methyl-3H-imidazolo[4,5-c]pyridinium-  
20 5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-  
3-cephem-4-carboxylate

25 syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-1H-imidazolo[4,5-c]pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1,2-dimethyl-1H-imidazolo[4,5-c]pyridinium-  
30 5-ylmethyl)-3-cephem-4-carboxylate

X-6050-(P')

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syn-7-[2-(2-Aminothiazole-4-yl)-2-methoxy-  
iminoacetamido]-3-(2,3-dimethyl-3H-imidazolo[4,5-c]-  
pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

5 syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-[2-(2-thienyl)-1H-imidazolo[4,5-c]-  
pyridinium-5-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazole-4-yl)-2-methoxy-  
iminoacetamido]-3-(2-phenyl-1H-imidazolo[4,5-b]-pyri-  
dinium-5-ylmethyl)-3-cephem-4-carboxylate

10 syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-(2-aminooxazolo[4,5-b]-pyridinium-  
4-ylmethyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-(2-methyloxazolo[4,5-c]-pyridinium-  
15 5-ylmethyl)-3-cephem-4-carboxylate or

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-(2-aminothiazolo[5,4-b]-pyridinium-  
4-ylmethyl)-3-cephem-4-carboxylate

or a pharmaceutically-acceptable salt or biologically-  
20 cleavable ester thereof.

8. A process as claimed in any one of claims 1  
to 6 for preparing

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-(thiazolo[4,5-c]-pyridinium-5-yl-  
25 methyl)-3-cephem-4-carboxylate

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-(2-methylthiazolo[4,5-c]pyridinium-  
5-ylmethyl)-3-cephem-4-carboxylate or

syn-7-[2-(2-aminothiazolo-4-yl)-2-methoxyimino-  
30 acetamido]-3-(2-methylthiazolo[5,4-c]pyridinium-5-yl-  
methyl)-3-cephem-4-carboxylate.

syn-7-[2-(2-Aminothiazol-4-yl)-2-methoxy-  
iminoacetamido]-3-(2-ethylthiazolo[4,5-c]pyridinium-5-  
ylmethyl)-3-cephem-4-carboxylate or a pharmaceutically-  
acceptable salt or biologically-cleavable ester thereof.

9. A compound of Formula (1), or a biologically-cleavable ester or pharmaceutically-acceptable salt thereof, whenever prepared according to a process as claimed in any one of claims 1 to 8.



(12)

# **EUROPEAN PATENT APPLICATION**

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(22) Date of filing: **09.10.84**

(51) Int. Cl.<sup>4</sup>: **C 07 D 501/46**  
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**C07D513/04**

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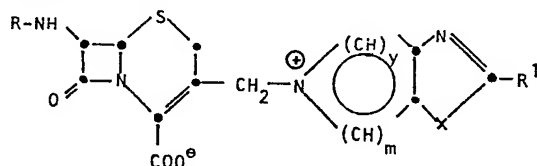
(71) Applicant: **ELI LILLY AND COMPANY**  
**307, East McCarty Street**  
**Indianapolis Indiana 46285(US)**

(72) Inventor: **Katner, Allen Samuel**  
**219 W. 81st Street**  
**Indianapolis Indiana 46260(US)**

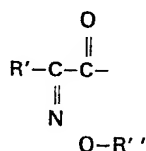
(74) Representative: **Hudson, Christopher Mark et al,**  
**Erl Wood Manor**  
**Windlesham Surrey GU20 6PH(GB)**

## (54) **Improvements on or relating to 3-bicyclicpyridinium-methyl cephalosporins.**

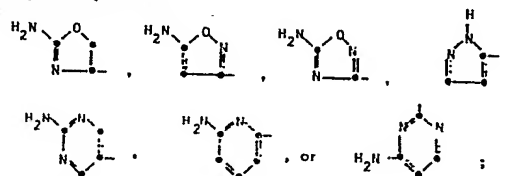
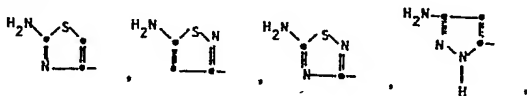
(57) Cephalosporin compounds substituted in the 7-position by a 2-(5- or 6-membered heterocyclic)-2-oximino-acetyl amino group and of the formula



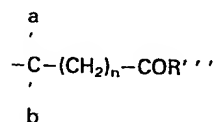
in which R is hydrogen, formyl,  $\alpha$ -aminoadipoyl, protected  $\alpha$ -aminoadipoyl, or an acyl group of the formula



in which R' is a 5- or 6-membered heterocyclic ring of the formulae



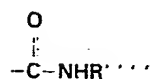
R' is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, a carboxy-substituted alkyl or carboxy-substituted cycloalkyl group of the formula:



in which n is 0-3; a and b when taken separately are, independently, hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, and when taken together with the carbon to which they are bonded form a C<sub>3</sub>-C<sub>7</sub> carbocyclic ring; R'' is hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, or OR<sup>o</sup>, in which R<sup>o</sup> is indanyl, phthalidyl, or an acyloxymethyl group of the formula -CH<sub>2</sub>-O-C(O)-R<sub>2</sub> in which R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or COOR<sup>o</sup> is a protected carboxy group;

./...

or R' ' is an N-substituted carbamoyl group of the formula



in which R' is C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl or C<sub>1</sub>-C<sub>3</sub> alkyl substituted by phenyl;

y and m, independently, are integers equal to 0, 1, 2 or 3, provided that y plus m equals 3;

R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, thienyl, amino or C<sub>1</sub>-C<sub>4</sub> alkanoylamino;

X is O, S or N-R<sup>2</sup>, where R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically-acceptable salt or biologically-cleavable ester thereof.



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	EP-A-0 064 740 (HOECHST) * Pages 89-98, claims, particularly claim 1, lines 14-21 *	1-11	C 07 D 501/46 // C 07 D 471/04 C 07 D 498/04 C 07 D 513/04
A	--- EP-A-0 074 268 (ELI LILLY) * Pages 57-62; claims *	1-11	
A	--- EP-A-0 088 320 (HOECHST) * Pages 63-71, claims, particularly page 64, lines 3-10 *	1-11	
P, X	--- EP-A-0 097 961 (BRISTOL-MYERS CO.) * Claims *	1-11	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 501/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11-12-1985	Examiner LUYTEN H.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

(19)



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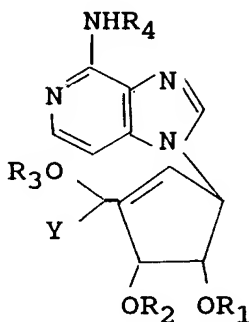
(11) Publication number:

**0 510 260 A2**

(12)

**EUROPEAN PATENT APPLICATION**(21) Application number: **91122405.3**(51) Int. Cl.<sup>5</sup>: **C07D 471/04, A61K 31/435,**  
**/(C07D471/04,235:00,221:00)**(22) Date of filing: **31.12.91**(30) Priority: **26.04.91 JP 122820/91**(43) Date of publication of application:  
**28.10.92 Bulletin 92/44**(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**(71) Applicant: **TOYO JOZO CO., LTD.**  
**632-1, Mifuku Ohito-cho**  
**Tagata-gun Shizuoka 410-23(JP)**(72) Inventor: **Obara, Takumi**  
**59-1, Odoi, Kannami-cho**  
**Tagata-gun, Shizuoka 419-01(JP)**  
Inventor: **Shuto, Satoshi**  
**690-10, Makinokou, Shuzenji-cho**  
**Tagata-gun, Shizuoka 410-24(JP)**  
Inventor: **Toriya, Minoru**  
**854-1, Mifuku, Ohito-cho**  
**Tagata-gun, Shizuoka 410-23(JP)**  
Inventor: **Fujiwara, Tatsuro**  
**310, Nirayama, Nirayama-cho**  
**Tagata-gun, Shizuoka 410-21(JP)**(74) Representative: **Wächtershäuser, Günter, Dr.**  
**Tal 29**  
**W-8000 München 2(DE)**(54) **6'-C-alkyl-3-deazaneplanocin A derivative and its preparation process and use.**

(57) Described herein are 6'-C-alkyl-3-deazaneplanocin A derivatives represented by the following formula:



wherein Y represents a lower alkyl group, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> individually mean a hydrogen atom or a hydroxyl-protecting group, and R<sub>4</sub> denotes a hydrogen atom or an amino-protecting group; their preparation processes; and antiviral agents containing them as an active ingredient.

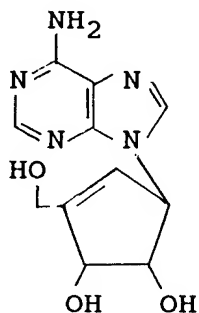
BACKGROUND OF THE INVENTION

## 1) Field of the Invention

This invention relates to novel derivatives of neplanocin A, and more specifically to neplanocin A derivatives useful as drugs, especially as antiviral agents and also to their preparation processes.

## 2) Description of the Related Art

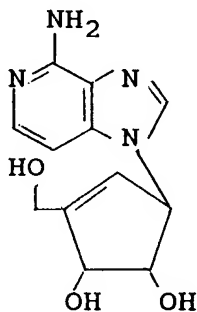
Neplanocin A is an antibiotic having antitumor activity and growth inhibitory activity for plant pathogenic fungi, i.e., filamentous fungi. It is produced by a microorganism, *Ampullariella sp.* A11079, and is represented by the following formula (IX):



(IX)

(Japanese Patent Appln. Laid-Open No. 154792/1979). It has recently been found that this compound also has antiviral activity (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 84-89, July 1985). Its use as an antiviral agent is therefore under investigation.

On the other hand, 3-deazaneplanocin A represented by the following formula (X):



(X)

is also known as a compound having antiviral activity [J. Med. Chem. **32**, 1442-1446 (1989)].

Neplanocin A and 3-deazaneplanocin A, however, tend to have high cytotoxicity compared to their antiviral activity. This has been an unignorable problem upon their use as drugs.

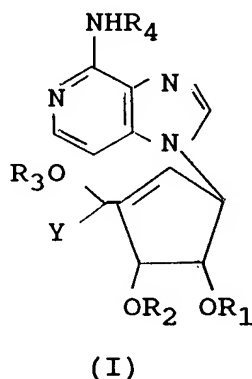
There is, therefore, an outstanding demand for the development of a compound having still higher antiviral activity but low cytotoxicity.

SUMMARY OF THE INVENTION

The present inventors have carried out an extensive investigation with a view toward overcoming the

above-described problems and obtaining a still better antiviral agent. As a result, it has been found that 6'-C-alkyl-3-deazaneplanocin A as represented by the following formula (I) have good antiviral activities but low cytotoxicity, leading to the completion of the present invention.

An object of the present invention is, therefore, to provide a 6'-C-alkyl-3-deazaneplanocin A derivative represented by the following formula (I):



wherein Y represents a lower alkyl group, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> individually mean a hydrogen atom or a hydroxyl-protecting group and R<sub>4</sub> denotes a hydrogen atom or an amino-protecting group, or a salt thereof.

Another object of the present invention is to provide a process for the preparation of the 6'-C-alkyl-3-deazaneplanocin A.

A further object of the present invention is to provide an antiviral agent comprising as an active ingredient the 6'-C-alkyl-3-deazaneplanocin A.

The 6'-C-alkyl-3-deazaneplanocin A derivatives according to this invention show excellent antiviral effects and, compared to neplanocin and the like, they have extremely low cytotoxicity and large chemotherapeutic indices. They can, therefore, be used advantageously as antiviral agents having high safety.

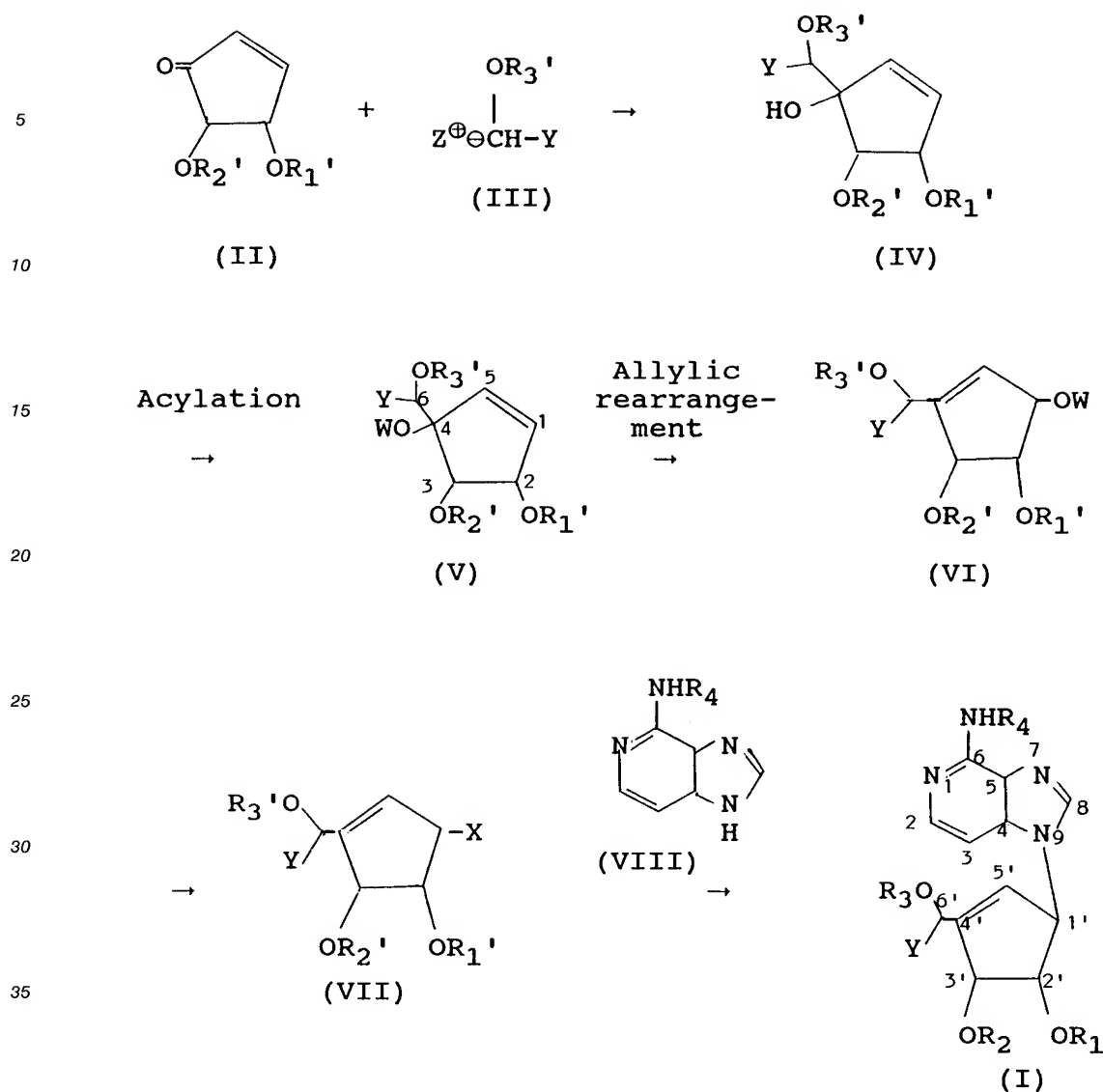
#### DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Examples of the lower alkyl group in the 6'-C-alkyl-3-deazaneplanocin A (I) of the present invention include normal or branched alkyl groups having about 1-4 carbon atoms. Specific examples include saturated alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and tert-butyl; halogen-containing alkyl groups such as trifluoromethyl, difluoromethyl, monofluoromethyl and trichloromethyl; and unsaturated alkyl groups such as ethenyl and ethynyl.

The 6'-C-alkyl-3-deazaneplanocin A (I) of the present invention can be prepared, for example, in any one of the following processes.

##### Process 1:

Following the below-described reaction scheme, a cyclopentenone derivative represented by the formula (II) and a compound represented by the formula (III) are reacted in an inert solvent so that a compound represented by the formula (IV) is obtained. The 4-hydroxyl group is then acylated to obtain a compound represented by the formula (V). After this compound (V) is then subjected to allylic rearrangement to form a compound represented by the formula (VI), the 1-substituent group of the compound (VI) is either substituted or converted to obtain a compound represented by the formula (VII). A 3-deazaadenine derivative represented by the formula (VIII) is reacted to the compound (VII) and, if desired, one or more of the protecting groups are eliminated from the reaction product, whereby the target compound, 6'-C-alkyl-3-deazaneplanocin A (I), is obtained.



wherein  $Y$ ,  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  have the same meanings as defined above,  $R_1'$ ,  $R_2'$  and  $R_3'$  individually mean a hydroxyl-protecting group,  $X$  is an electron-attracting eliminative group,  $W$  represents an acyl group, and  $Z$  denotes a counter-cation for stabilizing alkyl anions.

In the above reaction scheme, no particular limitation is imposed on the hydroxyl-protecting groups  $R_1'$ - $R_3'$ , the hydroxyl-protecting groups in  $R_1$ - $R_3$  and the amino-protecting group in  $R_4$ . In general, those employed in sugar or nucleic acid chemistry can be suitably chosen for use in the present invention. Further, the above hydroxyl-protecting groups may protect the hydroxyl groups either singly or in combination.

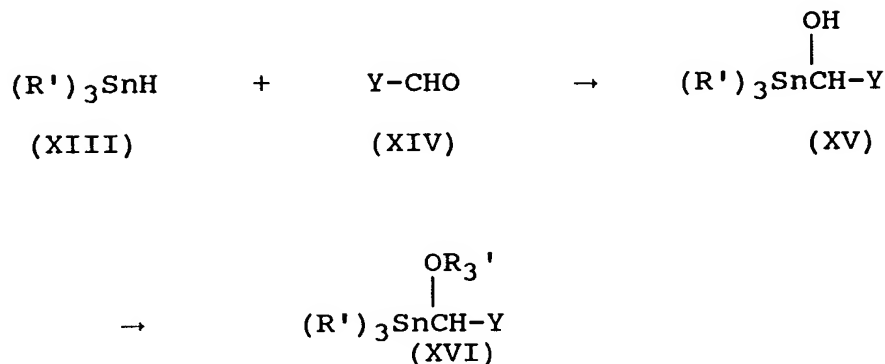
Particularly preferred examples of hydroxyl-protecting groups include those capable of simultaneously protecting the 2,3-diol groups of the compound (II), for example, isopropylidene and the like, and acetal-type protecting groups such as benzylidene and ethoxymethylene groups; and, in addition, silyl protecting groups such as *t*-butyldimethylsilyl and diisopropylmethylsilyl groups, and ether-type protecting groups such as benzyl and methoxymethyl groups.

Preferred examples of amino-protecting groups include those permitting easy introduction and de-protection, for example, acyl-protecting groups such as benzoyl and phthaloyl groups and urethane-type protecting groups such as benzyloxycarbonyl and *t*-butoxycarbonyl groups.

The starting material, the compound (II), can be obtained, for example, in accordance with the process described in Tetrahedron Lett. **31**, 1509-1512 (1990).

The counter-cation (Z) of the other starting material, the compound (III), is to stabilize an alkyl anion. Its examples include cations of metals having high ionization tendency. Specific examples include Li, Al, Zn, Mg, Ti and the like, with Li being especially preferred. The counter-cation may include one or more substituents, for example, alkyl groups or halogen atoms.

The compound (III) can be prepared, for example, in accordance with the following reaction scheme, namely, by reacting the aldehyde (XIV) with the alkyltin compound (XIII) in the presence of a strong base such as n-butyllithium, protecting the hydroxyl group of the resultant compound (XV) with the protecting group R<sub>3</sub>' to form the compound (XVI) and then reacting an alkyl metal compound such as n-butyl lithium with the compound (XVI).



wherein R' represents an alkyl group, and Y, R<sub>3</sub>' and Z have the same meanings as defined above. Examples of the hydroxyl-protecting group R<sub>3</sub>' include ether-type or silyl-type hydroxyl-protecting groups such as methoxymethyl, benzyl, p-methoxybenzyl, trityl, trimethylsilyl and t-butyldimethylsilyl.

The reaction between the compound (II) and the compound (III) can be conducted in an inert solvent. Illustrative of the inert solvent include ether solvents such as tetrahydrofuran and diethyl ether. In this reaction, the compound (III) is used generally in an amount at least equal to the equivalent(s) of the compound (II), preferably 1-2 times the equivalent(s) of the compound (II).

Although no particular limitation is imposed on the reaction temperature, the reaction can be conducted generally at room temperature or lower, preferably under cooling in a dry ice-acetone system. The reaction is carried out for a period from 1 hour to overnight, in general.

Next, the compound (IV) so obtained is acylated with a carboxylic acid or a carboxylic acid derivative such as a carboxylic ester, carboxylic halide or carboxylic anhydride in a manner known *per se* in the art.

No particular limitation is imposed on the acyl group (W) as long as the hydroxyl group acylated with the acyl group is allowed to undergo allylic rearrangement. Examples of the acyl group include acetyl, benzoyl and formyl groups. Of these, acetyl group is particularly preferred.

This acylation reaction can be conducted in the presence of a base such as 4-dimethylaminopyridine, pyridine, triethylamine or N,N-dimethylaniline, usually under heat, for several hours to a few days, in some instances for several ten days, in an inert solvent, for example, an ether solvent such as tetrahydrofuran (THF) or diethyl ether, a chlorohydrocarbon solvent such as methylene chloride or chloroform, an aromatic hydrocarbon solvent such as benzene or toluene or an aprotic solvent such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO) or acetonitrile. In this reaction, the carboxylic acid or its derivative can be used generally in an excess relative to the compound (IV), preferably in an amount 4-10 times the equivalent(s) of the latter. On the other hand, the base can be used generally in an amount about 8-20 times the equivalent(s) of the compound (IV).

The compound (V) obtained by the above acylation is then subjected to an allylic rearrangement reaction to provide the compound (VI) in which the 4-acyloxy group (WO) in the compound (V) has been rearranged to the 1-position.

This allylic rearrangement reaction can be conducted in an inert solvent, for example, an ether solvent such as THF or diethyl ether or an aromatic hydrocarbon solvent such as benzene or toluene while using, as a catalyst, at least one of Pd, Ni and Hg or a compound containing at least one of the above metals.

Preferred examples of the catalyst, namely, at least one of Pd, Ni and Hg or the compound containing at least one of the above metals are salts of divalent ions of these metals. Particularly preferred are palladium chloride, a dihalogenated palladium, and nickel dichloride, a dihalogenated nickel.

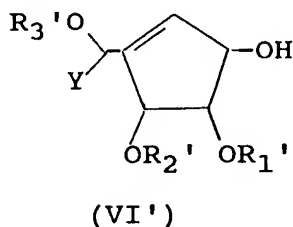


It is desirable for the allylic rearrangement reaction to use a suitable amount (for example, 0.01-0.5 equivalent) of a catalyst, preferably an appropriate amount (for example, 0.1-1 equivalent) of benzoquinone. The allylic rearrangement reaction can be conducted for about several hours under heat (for example, 60-100 °C or so).

The compound (VI) obtained as described above is then converted to the compound (VII) by replacing the 1-acyloxy group with the electron-attracting eliminative group (X).

Examples of the electron-attracting eliminative group (X) include sulfonyloxy groups such as p-toluenesulfonyloxy, methanesulfonyloxy and trifluoromethanesulfonyloxy; and halogen atoms. Preferred are p-toluenesulfonyloxy, methanesulfonyloxy and trifluoromethanesulfonyloxy groups.

Among the compounds (VII), the compounds in which X is a sulfonyloxy group can each be obtained by deacylating the 1-acyl group (W) of the compound (VI) to form the compound represented by the formula (VI'):



and then causing a sulfonyl chloride such as p-toluenesulfonyl chloride, methanesulfonyl chloride or trifluoromethanesulfonyl chloride on the compound (VI').

The deacylation reaction can be conducted generally by treating the compound (VI) at 0-40 °C or so, for 30 minutes to overnight, in the presence of about 2-5 equivalents of an inorganic base such as potassium carbonate, sodium hydrogencarbonate, sodium hydroxide or potassium hydroxide, in water or an alcohol solvent such as methanol or ethanol.

The reaction between the compound (VI') and the sulfonyl chloride can be conducted generally at 0-40 °C or so, for about 1-3 days, in the presence of a base such as triethylamine, 4-dimethylaminopyridine or pyridine, in an ether solvent such as THF or diethyl ether, a chlorohydrocarbon solvent such as methylene chloride or chloroform, an aromatic hydrocarbon solvent such as benzene or toluene or an aprotic solvent such as DMF, DMSO or acetonitrile.

On the other hand, the compound (VII) in which X is a halogen atom can be obtained by substituting the halogen atom for the hydroxyl group of the compound (VI') in accordance with a method known *per se* in the art, for example, in accordance with the method in which thionyl chloride is used or the method in which carbon tetrabromide and triphenylphosphine are used. As an alternative, an alkali halide (for example, NaI, LiI or KI) or the like may be reacted with the compound (VI).

The compound (VII) obtained as described above is finally reacted with the 3-deazaadenine derivative (VIII), whereby the target compound (I) of this invention can be obtained.

The above reaction is generally conducted by reacting, based on the compound (VII), about 2-5 equivalents of the 3-deazaadenine derivative (VIII) in the presence of 2-5 equivalents of a base and 1-2 equivalents of a crown ether at room temperature or under heat for 1 hour to 1 day or so in an inert solvent, for example, in an aprotic solvent such as DMF, DMSO, N,N-dimethylacetamide (DMA), acetonitrile or THF. In this reaction, sodium hydride, potassium carbonate or the like can be used as the base while 15-crown-5, 18-crown-6 or the like can be employed as the crown ether.

Incidentally, the 3-deazaadenine derivative (VIII) can be prepared by the process described in the literature, Chem. Pharm. Bull. 12, 866 (1964) or in a similar manner thereto. Although the 6-amino group of the compound may be protected, use of the compound without protection of the 6-amino group is preferred for conducting the reaction.

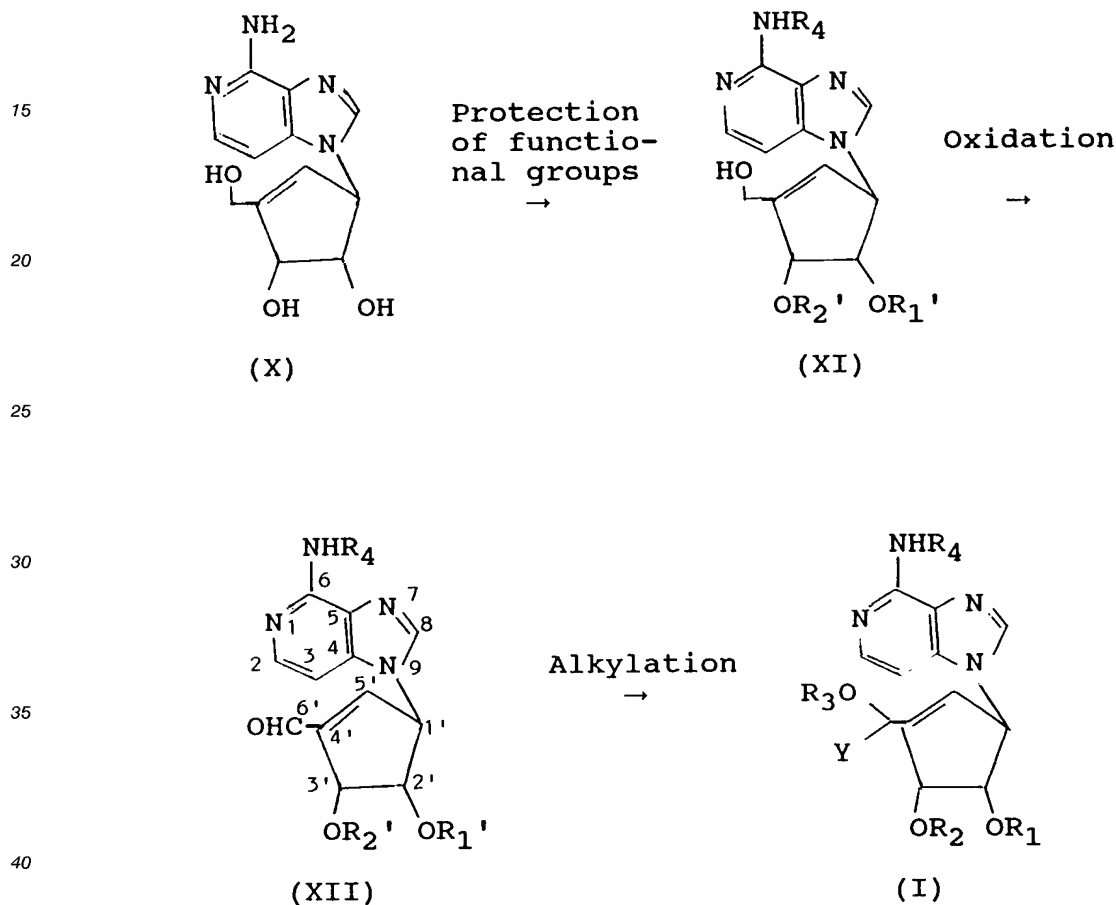
In the compound of this invention prepared as described above, the protecting groups of R<sub>1</sub>-R<sub>3</sub> and the protecting group in R<sub>4</sub> can be eliminated by a desired deprotecting reaction.

This deprotecting reaction can be carried out by reacting the compound with a mineral acid such as hydrochloric acid or sulfuric acid, an organic acid such as trifluoroacetic acid, a mineral acid-organic acid mixture such as HBr/acetic acid or HBr/trifluoroacetic acid, or a boron compound such as BBr<sub>3</sub> or BCl<sub>3</sub> or subjecting the compound to catalytic hydrogenation in the presence of a catalyst such as palladium or rhodium in water, an alcohol solvent such as methanol, a chlorohydrocarbon solvent such as methylene

chloride, an aromatic hydrocarbon solvent such as benzene or an ether solvent such as THF.

Process 2:

The 6'-C-alkyl-3-deazaneplanocin A (I) of this invention can be prepared, for example, following the reaction scheme, namely, by protecting the 6-amino group and 2'- and 3'-hydroxyl groups of 3-deazaneplanocin A (X) to form the amino-protected derivative (XI), oxidizing the derivative into the 6'-formyl derivative (XII), alkylating the formyl derivative with an alkylating reagent, and if desired, protecting the 6'-hydroxyl group or removing these protecting groups.



wherein  $R_1$  and  $R_2$  represent hydroxyl-protecting groups,  $R_3$  means a hydrogen atom or a hydroxyl-protecting group,  $R_4$  denotes a hydrogen atom or an amino-protecting group, and Y is a lower alkyl group.

In the above reaction scheme, no particular limitation is imposed on the protection of the amino group and hydroxyl groups of 3-deazaneplanocin A (X). Their protection can be effected usually by a method used in sugar or nucleic acid chemistry.

In particular, it is preferred to choose the amino-protecting group for  $R_4$ . Examples of preferred amino-protecting groups are those remaining stable under oxidizing and alkylating reaction conditions and permitting easy introduction and deprotection, including acyl-protecting groups such as benzoyl and phthaloyl groups and urethane-type protecting groups such as benzyloxycarbonyl and t-butoxycarbonyl groups.

Preferred hydroxyl-protecting groups include protecting groups capable of simultaneously protecting the 2'- and 3'-hydroxyl groups, such as isopropylidene, benzylidene and ethoxymethylene groups; and silyl protecting groups such as t-butyldimethylsilyl and diisopropylmethylsilyl groups, and ether-type protecting groups such as benzyl and methoxymethyl groups.

The oxidation of the amino-protected derivative (XI) can be effected in an inert solvent, using an

oxidizing agent such as an oxidizing agent of the chromic acid or manganic acid type. Namely, the oxidation reaction can be conducted at a temperature ranging from room temperature to the reflux temperature in a chlorohydrocarbon solvent such as methylene chloride, chloroform or dichloroethane, using an excess amount of an oxidizing agent such as  $\text{MnO}_2$  or  $\text{BaMnO}_4$ .

5 The 6'-formyl derivative (XII) obtained by the above-described oxidation reaction is alkylated further and, if necessary, its 6'-hydroxyl group is protected or such protecting groups are removed, whereby the 6'-C-alkyl-3-deazaneplanocin A (I) according to this invention can be obtained.

The alkylating reaction can be effected by reacting the 6'-formyl derivative (XII) with an alkylating reagent, for example, a Grignard reagent such as methylmagnesium bromide or ethylmagnesium bromide, 10 an alkyllithium such as methyllithium or ethyllithium, a trialkylaluminum such as trimethylaluminum or triethylaluminum, an organotitanium reagent such as trimethoxymethyltitanium and dichlorodimethyltitanium or an organozinc reagent such as dimethylzinc or diethylzinc in a chlorohydrocarbon solvent such as methylene chloride, an ether solvent such as THF or a hydrocarbon solvent such as hexane.

The protection of the 6'-hydroxyl group of the compound obtained by the alkylation of the 6'-formyl 15 derivative (XII) can be conducted in a similar manner to the above-described case of  $\text{R}_3\text{C}$ . As an alternative, it can also be effected with an acyl group such as an acetyl or benzoyl group by a method employed in sugar or nucleic acid chemistry.

Further, the removal of the amino-protecting and hydroxyl-protecting groups from the compound obtained by the alkylation can be conducted generally by a method used in sugar or nucleic acid 20 chemistry.

To collect the thus-prepared 6'-C-alkyl-3-deazaneplanocin A (I) from the reaction mixture, conventional separating and purification methods can be used. The compound (I) can be separated and purified by column chromatography, namely, by distilling off the solvent employed in the reaction, dissolving the residue in a solvent such as methanol, adsorbing the compound on an adsorbent such as silica gel and 25 then eluting it with an elution solvent such as a chloroform-methanol solvent system.

The 6'-C-alkyl-3-deazaneplanocin A (I) can be converted to pharmaceutically-acceptable, non-toxic salts as needed, by a method known *per se* in the art.

Examples of such salts include inorganic acid salts such as the hydrochloride, sulfate and phosphate; and organic acid salts such as the acetate, propionate, tartrate, citrate, glycolate, gluconate, succinate, 30 malate, glutamate, aspartate and methanesulfonate.

The 6'-C-alkyl-3-deazaneplanocin A (I) according to this invention contains some asymmetric carbons and hence includes isomers with respect to the asymmetric carbons. These isomers are all embraced by the present invention.

Incidentally, the compound (V) in Process 1 has two isomers with respect to the 6-position. The 35 compound of this invention derived from one of these isomers, said isomer having a lower  $R_f$  in silica gel TLC, is preferred as its antiviral activity are superior. Further, it is generally preferable that, in the compound (VII), the group X at the 1-position is in the  $\alpha$  configuration. The group X may, however, be either in the  $\alpha$  configuration or in the  $\beta$  configuration as long as the protecting group  $\text{R}_1$  for the second position is an acyl group.

40 To use the invention compound (I) or its salt as an antiviral agent, it is only necessary to administer an effective amount of the compound (I) or its salt as is or after formulating the same together with a known carrier into a dosage form.

Usable administration methods include oral administration or parenteral administration (for example, injection such as intravascular, intramuscular, subcutaneous or intraperitoneal administration; rectal admin- 45 istration; transocular administration; or the like). The above-mentioned formulation can be conducted depending on the administration method. Dosage forms include, for example, tablets, pills, powder, granules, capsules, injection, suppositories and eye drop. For their formulation, various carriers corresponding to the individual dosage forms can be used. For example, oral preparations such as tablets, granules and capsules can use excipients such as starch, lactose, sucrose, mannitol, carboxymethylcellulose, corn 50 starch and inorganic salts; binders such as starch, dextrin, gum arabic, gelatin, hydroxypropylstarch, methylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, crystalline cellulose, ethylcellulose, polyvinyl pyrrolidone and macrogol; disintegrators such as starch, hydroxypropylstarch, carboxymethylcellulose, sodium carboxymethylcellulose and hydroxypropylcellulose; surfactants such as sodium lauryl sulfate, soybean lecithin, sucrose fatty acid ester and Polysolvate 80; lubricants such as talc, wax, a 55 hydrogenated vegetable oil, sucrose fatty acid ester, magnesium stearate and calcium stearate; fluidity promoters; corrigents; colorants; and perfumes.

The invention compound (I) or its salt can also be used in the form of a suspension, emulsion, syrup or elixir.

A parenteral preparation can generally use, as a diluent, a distilled water for injection, physiological saline, an aqueous glucose solution, a vegetable oil for injection, propylene glycol, polyethylene glycol or the like. Further, antiseptic, preservative and/or stabilizer can also be added as needed. From the safety standpoint, it is also possible to fill and lyophilize the parenteral preparation in a vial or the like and, immediately before use, to reconstitute it with a diluent. In addition, isotonicity, stabilizer, preservative, soothing agent and the like can also be incorporated suitably as needed.

The dose of the invention compound (I) or its salt varies depending on the administration route, the age, body weight and conditions of the patient, etc. In general, the daily dose may be about 5 mg to 1 g, preferably about 25-500 mg per adult in term of the compound (I). It is administered in 1-3 portions.

One of 6'-C-alkyl-3-deazaneplanocin As (I) which had been obtained as described above was tested for their pharmacological effects. The results will be described next.

#### (1) Antiviral activity:

By partly modifying the testing method reported in Antimicrobial Agents and Chemotherapy, **24**(3), 353-361 (1983), antiviral activity was analyzed in the following manner. 200  $\mu$ l of Eagle's minimum essential medium (with 10% fetal calf serum), in which Vero cells (product of Flow General Inc., marketed by Dainippon Pharmaceutical Co., Ltd., available from National Institute of Health) were suspended at the concentration of  $3 \times 10^5$  cells/ml, were cultured in a 98-well flat bottom plate. Subsequent to dense monolayer culture, the medium was removed and 90  $\mu$ l of Eagle's minimum essential medium (with 3% fetal calf serum) containing a test compound were added. The tissue culture infections dosis 50% (TCID<sub>50</sub>) had been determined in advance without addition of any drug. The above-prepared culture plate was inoculated with 10  $\mu$ l of a virus solution whose concentration was 100 times higher than TCID<sub>50</sub> determined in advance. The cells were cultured for 36 hours at 37 °C under 5% CO<sub>2</sub>. The cytopathic effect (CPE) was microscopically observed, whereby the minimum virus growth inhibitory concentration (MIC) was determined. The results are shown in Table 1.

#### (2) Measurement of cytotoxicity:

Added to 100  $\mu$ l of Eagle's minimum essential medium were 100  $\mu$ l of Eagle's minimum essential medium (with 10% fetal calf serum), in which Vero cells were suspended at the concentration of  $5 \times 10^4$  cells/ml as well as a test compound. The resultant mixture was cultured for 72 hours in a 98-well flat bottom plate. The cytotoxicity of the test compound was then measured by the MTT measuring method reported in J. Immunol. Methods, **65**, 55-63 (1983). The cytotoxicity is indicated in terms of the concentration (ID<sub>50</sub>) which inhibited the growth of cells to 50%.

These results are summarized in Table 1.

Table 1

Test compound	Minimum virus growth inhibitory concn. ( $\mu$ g/ml)	Minimum cytotoxicity concn. ( $\mu$ g/ml)	Chemotherapeutic index (MTC/MIC)
6'-c-Methyl-3-deazaneplanocin A	1.0	12.4	12.4
3-Deazaneplanosin A	0.24	0.55	2.3
Neplanocin A	0.24	0.26	1.1

As is apparent from the results of the above-described tests on pharmacological activities, the 6'-C-alkyl-3-deazaneplanocin As (I) of the present invention show excellent antiviral activity and, compared to neplanocin A, their cytotoxicity are extremely low and their chemotherapeutic indices are great. As is also evident from the fact that no case of death was observed by 200 mg/kg oral administration of the above compound to mice, the 6'-C-alkyl-3-deazaneplanocin As (I) of the present invention have high safety and can hence be used effectively as antiviral agents.

The present invention will next be described in further detail by the following examples. It should, however, be borne in mind that the present invention is not limited at all by the following examples. In the following examples, "Merck Art. 9385 silica gel" (trade name) was used in silica gel flash columns.

#### Referential Example 1

## Synthesis of [1-(methoxymethoxy)ethyl]tributyltin

Diisopropylamine (32 mL, 230 mmol) was added to 400 mL of dry tetrahydrofuran (THF), followed by stirring at 0 °C. The resultant mixture was added dropwise at the same temperature to 125 mL (200 mmol) of a 1.6 M butyllithium-hexane solution, followed by the dropwise addition of 52.8 mL (200 mmol) of tributyltin hydride at the same temperature upon an elapsed time of 5 minutes. Fifteen minutes later, the reaction mixture was cooled to -76 °C, to which a solution of 11.2 mL (200 mmol) of acetaldehyde in 50 mL of dry THF was added dropwise. Thirty minutes later, 100 mL of a saturated aqueous ammonium chloride solution were added to the reaction mixture, and the reaction mixture was then poured into 250 mL of hexane. The hexane layer was washed twice with 500-mL portions of water. After dried over sodium sulfate, the hexane solution was filtered through a "Whatman Filter Paper Ips" (trade name, product of Whatman Company) and the resulting filtrate was concentrated under reduced pressure. The residue so obtained was dissolved in 50 mL of dry methylene chloride, to which 100 mL (790 mmol) of N,N-dimethylaniline were added. The resultant solution was stirred at 0 °C, followed by the dropwise addition of 22.8 mL (300 mmol) of chloromethyl methyl ether. The temperature of the reaction mixture was allowed to rise to room temperature, at which the reaction mixture was stirred overnight. The reaction mixture was then poured into 2 L of hexane. The organic layer was washed with chilled 0.5N-HCl (500 mL x 2), chilled water (500 mL x 1) and a chilled, saturated, aqueous sodium hydrogencarbonate solution (500 mL x 2). The organic layer was then filtered through a "Whatman Filter Paper Ips", followed by concentration under reduced pressure. The residue so obtained was purified by flash chromatography on a silica gel column [silica gel: 500 g; eluted with hexane → hexane-ethyl acetate (25:1)], whereby the title compound was obtained as a yellow syrup. Yield: 27.8 g (yield: 38%).

## Example 1

## Synthesis of (2S,3S,4S)-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-hydroxy-5-cyclopentene

[1-(Methoxymethoxy)ethyl]tributyltin (21.7 g, 60 mmol) prepared in Referential Example 1 was added to 240 mL of dry THF. After the resultant solution was cooled under stirring to -79 °C, a solution of 1.6 M of n-butyllithium in 37.4 mL (60 mmol) of hexane was added dropwise to the solution. Twenty minutes later, a solution of 7.37 g (48 mmol) of (2S,3S)-2,3-(isopropylidenedioxy)-5-cyclopentene-4-one, which had been prepared in accordance with Tetrahedron Lett., **31**, 1509-1512 (1990), in 60 mL of dry THF was added dropwise at -78 °C to the reaction mixture. After they were reacted for 2.5 hours at the same temperature, 2L of chloroform were added to the reaction mixture, followed by the further addition of 400 mL of water. The resultant mixture was allowed to separate into layers. After the chloroform layer was filtered through a "Whatman Filter Paper Ips", the resulting filtrate was concentrated under reduced pressure. The residue so obtained was purified by flash chromatography on a silica gel column [silica gel: 400 g; eluted with hexane-acetone (25:1)], whereby the title compound was obtained as a clear syrup. Yield: 10.6 g (90%). MASS, FAB (Pos.) m/e: 245 (MH<sup>+</sup>).

## Example 2

## Synthesis of (2S,3S,4S)-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-acetoxy-5-cyclopentene

(2S,3S,4S)-2,3-(Isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-hydroxy-5-cyclopentene (5.93 g, 24.3 mmol) was added to 100 mL of methylene chloride. The resultant mixture was stirred at room temperature, to which 9.17 mL (97.2 mmol) of acetic anhydride, 2.97 g (24.3 mmol) of 4-dimethylaminopyridine (DMAP) and 13.55 mL (97.2 mmol) of triethylamine were added. After the mixture was stirred at room temperature for 10 days, the reaction mixture was added to 400 mL of chloroform, followed by washing with 80 mL of water. The organic layer was filtered through a "Whatman Filter Paper Ips" and the filtrate was concentrated under reduced pressure. The residue so obtained was purified by flash chromatography on a silica gel column [silica gel: 90 g; eluted with hexane-ethyl acetate (6:1)], whereby two types of diastereomers of the title compound, said diastereomers having different configurations at the 6-position, were obtained as syrups, respectively, including 3.7 g (yield: 53%) of a stereoisomer having a higher R<sub>f</sub> value [R<sub>f</sub>: 0.38; silica gel TLC plate "Art. 5715", product of Merck & Co., Inc.; hexane-ethyl acetate (3:1)] and 2.0 g (yield: 29%) of a stereoisomer having a lower R<sub>f</sub> value [R<sub>f</sub>: 0.32; hexane-ethyl acetate (3:1)]. Both the stereoisomers had the following mass spectrum. MASS, CI (Pos.) m/e: 287 (MH<sup>+</sup>).

## Example 3

Synthesis of (1S,2S,3R)-1-acetoxy-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-cyclopentene

- 5 Added to 50 ml of dry THF were 1.55 g (54.2 mmol) of (2S,3S,4S)-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-acetoxy-5-cyclopentene [the compound having the lower R<sub>f</sub> value (R<sub>f</sub> = 0.32)] which was the compound obtained in Example 2. Further, 71 mg (0.27 mmol) of PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> and 235 mg (2.17 mmol) of 1,4-benzoquinone were added, followed by overnight reflux under an argon gas atmosphere. The reaction mixture was concentrated under reduced pressure. The residue so obtained was  
 10 purified by flash chromatography on a silica gel column [silica gel: 100 g; eluted with hexane-ethyl acetate (5:1)], whereby 484 mg of the title compound were obtained as a syrup (yield: 31%). Further, 692 mg of the starting material were recovered (recovery rate: 45%).  
 MASS, FAB (Pos.) m/e: 287 (MH<sup>+</sup>).

## 15 Example 4

Synthesis of (1S,2S,3R)-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-1-hydroxy-4-cyclopentene

- (1S,2S,3R)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-cyclopentene (440 mg,  
 20 1.54 mmol) obtained above in Example 3 was dissolved in 10 ml of dry methanol, followed by the addition of 425 mg (3.08 mmol) of anhydrous potassium carbonate. The resulting mixture was stirred at room temperature for 5.5 hours. The reaction mixture was concentrated under reduced pressure and then dissolved in 100 ml of chloroform. After the chloroform solution was washed with an aqueous solution of sodium chloride, the chloroform layer was filtered through a "Whatman Filter Paper lps" and the filtrate was  
 25 concentrated under reduced pressure. The residue so obtained was purified by flash chromatography on a silica gel column (silica gel: 20 g; eluted with hexane-ethyl acetate (3:1)), whereby 346 mg of the title compound were obtained as a syrup (yield: 92%).  
 MASS, FAB (Pos.) m/e: 245 (MH<sup>+</sup>).

## 30 Example 5

Synthesis of (1S,2S,3R)-1-[(p-toluenesulfonyl)oxy]-2,3-(isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-4-cyclopentene

- (1S,2S,3R)-2,3-(Isopropylidenedioxy)-4-[1-(methoxymethoxy)ethyl]-1-hydroxy-4-cyclopentene (313 mg,  
 35 1.29 mmol) obtained above in Example 4 was stirred in 8 ml of dry methylene chloride, followed by the addition of 489 mg (2.57 mmol) of p-toluenesulfonyl chloride and 715  $\mu$ l (5.14 mmol) of triethylamine. While shielding light, the resulting mixture was stirred for 2 days at room temperature. Water (20 ml) was added to the reaction mixture, followed by the addition of 50 ml of chloroform. The mixture thus formed  
 40 was allowed to separate into layers. After the organic layer was filtered through a "Whatman Filter Paper lps", the resultant filtrate was concentrated under reduced pressure. The residue so obtained was purified by flash chromatography on a silica gel column [silica gel: 40 g; eluted with hexane-ethyl acetate (5:1)], whereby 382 mg of the title compound were obtained as a syrup.  
 MASS, FAB (Pos.) m/e: 399 (MH<sup>+</sup>).  
 45 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ :  
 7.86(d), 7.33(d), 5.61(s), 5.20(m), 4.85(d), 4.72(t), 4.59(q), 4.46(q), 3.34(s), 2.45(s), 1.40-1.25(m).

## Example 6

- 50 Synthesis of 2',3'-O-isopropylidene-6'-C-methyl-6'-O-(methoxymethyl)-3-deazaneplanocin A

- 3-Deazadenine (202 mg, 1.5 mmol) was added to 2 ml of dry DMF, followed by stirring. Then, 72.4 mg (1.5 mmol) of 50% NaH (in oil) were added at room temperature and 150  $\mu$ l (0.75 mmol) of 15-crown-5 were added further. The resultant mixture was stirred for one hour. Added to the reaction mixture was a  
 55 solution of 300 mg (0.75 mmol) of the tosylate obtained in Example 5. After the reaction system was purged with argon gas, the reaction mixture was stirred at 80 °C. Two hours later, the reaction mixture was cooled down to room temperature and was then concentrated under reduced pressure. Ethyl acetate (100 ml) was added to the residue so obtained, and insoluble matter was filtered off. The filtrate was washed with an

aqueous solution of sodium chloride. The ethyl acetate layer was filtered through a "Whatman Filter Paper lps", and the filtrate was concentrated under reduced pressure. The residue so obtained was purified by flash chromatography on a silica gel column [Art. 9385: 40 g; eluted with  $\text{CHCl}_3$ -MeOH-conc.  $\text{NH}_4\text{OH}$  (40:1:0.1)], whereby 150 mg of the title compound were obtained as crystals (yield: 55%).

5 MASS, FAB (Pos.) m/e: 361 ( $\text{MH}^+$ ).

#### Example 7

#### Synthesis of 6'-C-Methyl-3-deazaneplanocin A

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A protected derivative (150 mg, 0.42 mmol) of 2',3'-O-isopropylidene-6'-C-methyl-6'-O-(methoxymethyl)-3-deazaplanocin A obtained above in Example 6 was added to 5 ml of a 5M HCl-methanol solution. One hour later, the reaction mixture was concentrated. Several milliliters of methanol were added to the residue so obtained, followed again by concentration under reduced pressure. That  
 15 procedure was repeated three times. Methanol was added to the residue so obtained. The methanol solution was adjusted to pH 10 with concentrated liquid ammonia, followed by concentration under reduced pressure. Ethanol was added, followed by concentration under reduced pressure. This procedure was repeated three times. The residue was dissolved in ethanol and then caused to be adsorbed on 500 mg of silica gel, followed by purification by flash chromatography on a silica gel column [silica gel: Art. 9385 - 10 g; eluted with  $\text{CHCl}_3$ -MeOH-concentrated  $\text{NH}_4\text{OH}$  (65:25:2)], whereby 100 mg of the title compound were  
 20 obtained as crystals (yield: 87%).

The compound was recrystallized from ethanol so that prism crystals were obtained:

MASS, FAB (Pos.) m/e: 277 ( $\text{MH}^+$ ).

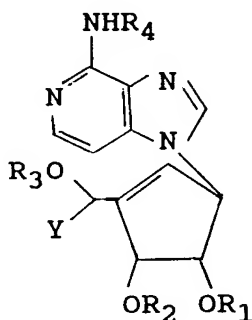
NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ :

25 8.17(s), 7.65(d), 7.09(d), 5.96(s), 5.42(m), 4.62(d), 4.56(q), 4.16(t), 1.44(d).

#### Claims

1. A 6'-C-alkyl-3-deazaneplanocin A derivative represented by the following formula (I):

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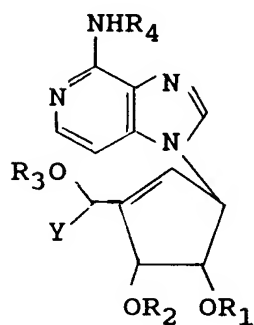
(I)

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wherein Y represents a lower alkyl group,  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$  individually mean a hydrogen atom or a hydroxyl-protecting group and  $\text{R}_4$  denotes a hydrogen atom or an amino-protecting group, or a salt thereof.

50 2. A process for the preparation of a 6'-C-alkyl-3-deazaneplanocin A derivative of the following formula (I):

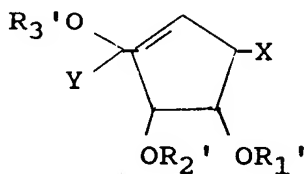
55



(I)

wherein Y represents a lower alkyl group, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> individually mean a hydrogen atom or a hydroxyl-protecting group and R<sub>4</sub> denotes a hydrogen atom or an amino-protecting group, or a salt thereof, which comprises:

reacting in an inert solvent a cyclopentene derivative of the following formula (VII):



(VII)

wherein Y has the same meaning as defined above, R<sub>1</sub>', R<sub>2</sub>' and R<sub>3</sub>' individually mean a hydroxyl-protecting group and X denotes an electron-attracting eliminative group, with a 3-deazadenine derivative of the following formula (VIII):

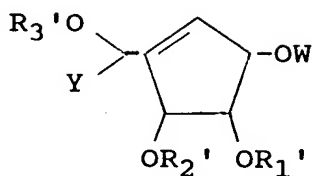


(VIII)

wherein R<sub>4</sub> has the same meaning as defined above; and, if desired, removing one or more of the protecting groups from the reaction product.

3. The process of claim 2, wherein the cyclopentene derivative represented by the formula (VII) has been obtained by substituting or converting in an inert solvent a compound of the following formula (VI):

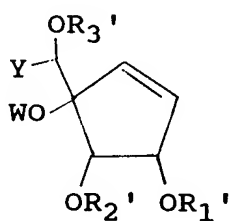




(VI)

wherein Y represents a lower alkyl group,  $R_1'$ ,  $R_2'$  and  $R_3'$  individually mean a hydroxyl-protecting group and W denotes an acyl group.

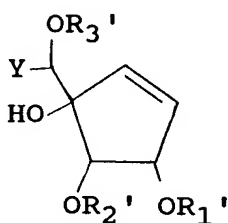
4. The process of claim 3, wherein the compound of the formula (VI) has been obtained by subjecting a compound of the following formula (V):



(V)

wherein Y represents a lower alkyl group,  $R_1'$ ,  $R_2'$  and  $R_3'$  individually mean a hydroxyl-protecting group and W denotes an acyl group, to allylic rearrangement in an inert solvent in the presence of a catalyst selected from the group consisting of at least one of Pd, Ni and Hg and compounds comprising at least one of Pd, Ni and Hg.

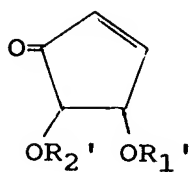
5. The process of claim 4, wherein the compound of the formula (V) has been obtained by subjecting a compound of the following formula (IV):



(IV)

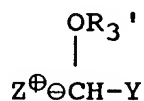
wherein Y represents a lower alkyl group and  $R_1'$ ,  $R_2'$  and  $R_3'$  individually mean a hydroxyl-protecting group, to acylation in an inert solvent.

6. The process of claim 5, wherein the compound of the formula (IV) has been obtained by reacting in an inert solvent a cyclopentenone derivative of the following formula (II):



(II)

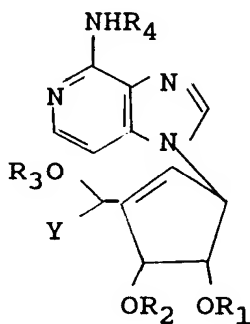
wherein  $R_1$  and  $R_2$  individually mean a hydroxyl-protecting group, with a compound of the following formula (III):



(III)

wherein Y represents a lower alkyl group,  $R_3$  means a hydroxyl-protecting group and Z denotes a counter-cation for stabilizing an alkyl anion.

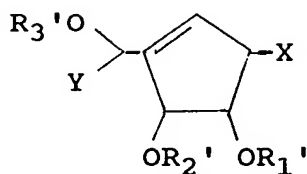
7. An antiviral agent comprising as an active ingredient a 6'-C-alkyl-3-deazaneplanocin A derivative represented by the following formula (I):



(I)

wherein Y represents a lower alkyl group,  $R_1$ ,  $R_2$  and  $R_3$  individually mean a hydrogen atom or a hydroxyl-protecting group and  $R_4$  denotes a hydrogen atom or an amino-protecting group, or a salt thereof.

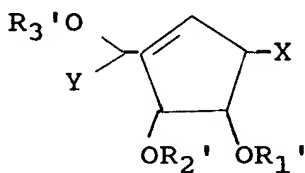
8. A cyclopentene derivative represented by the following formula (VII):



(VII)

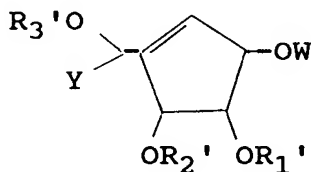
wherein Y represents a lower alkyl group,  $R_1'$ ,  $R_2'$  and  $R_3'$  individually mean a hydroxyl-protecting group and X denotes an electron-attracting eliminative group.

9. A process for the preparation of a cyclopentene derivative represented by the following formula (VII):



(VII)

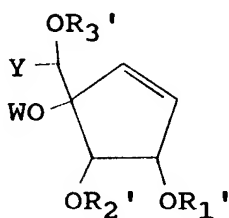
wherein Y represents a lower alkyl group,  $R_1'$ ,  $R_2'$  and  $R_3'$  individually mean a hydroxyl-protecting group and X denotes an electron-attracting eliminative group, which comprises substituting or converting in an inert solvent a compound represented by the following formula (VI):



(VI)

wherein Y,  $R_1'$ ,  $R_2'$  and  $R_3'$  have the same meanings as defined above and W denotes an acyl group.

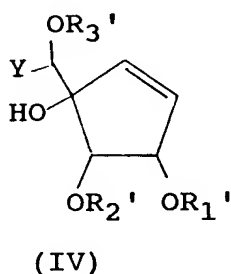
10. The process of claim 9, wherein the compound represented by the formula (VI) has been obtained by subjecting a compound, which is represented by the following formula (V):



(V)

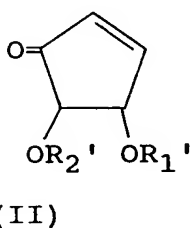
wherein Y represents a lower alkyl group,  $R_1$ ,  $R_2$  and  $R_3$  individually mean a hydroxyl-protecting group and W denotes an acyl group, to allylic rearrangement in an inert solvent in the presence of a catalyst selected from the group consisting of at least one of Pd, Ni and Hg and compounds comprising at least one of Pd, Ni and Hg.

11. The process of claim 10, wherein the compound represented by the formula (V) has been obtained by subjecting a compound of the following formula (IV):

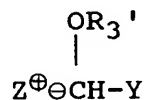


wherein Y represents a lower alkyl group and  $R_1$ ,  $R_2$  and  $R_3$  individually mean a hydroxyl-protecting group, to acylation in an inert solvent.

12. The process of claim 11, wherein the compound represented by the formula (IV) has been obtained by reacting in an inert solvent a cyclopentenone derivative of the following formula (II):



wherein  $R_1$  and  $R_2$  individually mean a hydroxyl-protecting group, with a compound of the following formula (III):



wherein Y represents a lower alkyl group,  $R_3$  means a hydroxyl-protecting group and Z denotes a counter-cation for stabilizing an alkyl anion.